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below. A slow pulse initially, a slight increase in the pulse rate on standing and after exercise, a quick fall in pulse rate after exercising, and a rise in systolic blood pressure on standing raise the index.

TABLE I
POINTS OF GRADING CARDIOVASCULAR CHANGES (SCOTT³)

A. RECLINING PULSE RATE (POINTS)		B. PULSE RATE INCREASE ON STANDING (POINTS)				
		0-10	11-18	19-26	27-34	35-42
50- 60	3	3	3	2	1	0
61- 70	3	3	2	1	0	-1
71- 80	2	3	2	0	-1	-2
81- 90	1	2	1	-1	-2	-3
91-100	0	1	0	-2	-3	-3
101-110	-1	0	-1	-3	-3	-3
C. STANDING PULSE RATE (POINTS)		D. PULSE RATE INCREASE IMMEDIATELY AFTER EXERCISE (POINTS)				
		0-10	11-20	21-30	31-40	41-50
60- 70	3	3	3	2	1	0
71- 80	3	3	2	1	0	0
81- 90	2	3	2	1	0	-1
91-100	1	2	1	0	-1	-2
101-110	1	1	0	-1	-2	-3
111-120	0	1	-1	-2	-3	-3
121-130	0	0	-2	-3	-3	-3
131-140	-1	0	-3	-3	-3	-3
E. RETURN OF PULSE RATE TO STANDING NORMAL AFTER EXERCISE (POINTS)		F. SYSTOLIC PRESSURE STANDING COMPARED WITH RECLINING				
0- 30 seconds	3	Rise of 8 mm. or more				3
31- 60 seconds	2	Rise of 2-7 mm.				2
61- 90 seconds	1	No rise				1
91-120 seconds	0	Fall of 2-5 mm.				0
After 120 seconds; 2-10 beats above	-1	Fall of 6 mm. or more				-1
11-30 beats above normal	-2					

The Schneider method of testing was revised in 1923,⁴ and has had wide use in the examination of men applying for admission to the aviation services.

The diurnal variations in the total score were ascertained by Schneider⁴ on seven men and seven women. The test was made hourly, and the subjects were kept busy between tests with desk work. They ate the usual meals. The mean score for the men for the twenty-four hours ranged from 10.1 to 13.6, and for the women, from 9 to 14. The largest variations followed eating. The score rose rapidly from 9 A.M. to noon, declined after lunch to 2 P.M., and then rose again until 5 P.M. The evening meal caused another fall. From 8 P.M. to 2 A.M. the index rose, reaching the maximum at 2 A.M. After this there was a slight fall. The effect of conscientious physical training is a higher score. In a study of a football squad by Schneider,⁴ the index was lower after discon-

tinuance of training because of acceleration of the heart. Grant⁶ states that this test gives an estimate of the efficiency of the cardiovascular system. The average index of commercial air pilots is 14.⁶

The use of this test is dual, i.e., it can be employed both as a screening test and as a method of periodic checkup. Schneider,¹ Armstrong,⁷ and Scott³ caution the student of the subject against drawing conclusions from the test alone, without evaluating all other methods of examination. Likewise, army and navy regulations state that a low index alone is insufficient for disqualification. The scoring is lowered by previous exercise, emotion, infection, excesses of any sort, and by physical deficiencies. Ingestion of food, fatigue, and careless testing affect the score.

Schneider has tested large numbers of normal men, and Scott³ suggested the following interpretation of scores: excellent, 14-18; very good, 11-13; fair, 9-10; doubtful, 7-8; and unsatisfactory, below 7.

The test must be carefully done. The subject and the examiner must be alone in a quiet room. The preliminary rest must be provided on a comfortable couch or bed. Due consideration to the ingestion of food or liquor, smoking, recent illness, emotion, and fatigue must be given. And, finally, the examiner must appreciate that any test, when taken for the first time, may be poorly performed even by men and women in excellent physical condition, so important are the emotional influences of fear and anxiety.

In the present conflict, with the great demand for large numbers of air recruits, it is most important that unfit men be rejected, and equally important that favorable prospects be accepted. Inasmuch as the Schneider test is widely employed in the examination of aviation recruits, it is important to re-emphasize the limitations of the test.

A careful search of the literature has not revealed any application of the test to patients with known cardiovascular defects. The present observations were undertaken to supply these data.

TABLE II
NORMAL CONTROLS

INSTITUTION	NO.	AGE RANGE	SCORE RANGE	AVERAGE	STANDARD DEVIATION
University School	11	16 to 19	0 to 15	6.91	4.032
Western Reserve	97	18 to 32	2 to 17	10.88	3.328
Lakeside staff	17	23 to 53	6 to 16	12.94	2.775
Miscellaneous	6	15 to 38	0 to 17	10.0	6.0
Women	7	22 to 30	-2 to 18	8.71	6.315
Total	138	15 to 53	-2 to 18	10.68	3.966

Normal Controls.—In order to familiarize ourselves with the index, several groups of normal persons were tested: 138 young, normal adults in all. The scores are tabulated in Table II.

The tests on the seventeen members of the staff of Lakeside Hospital were especially valuable because there was no emotional factor. In this group the average resting pulse rate was 74; the average increase

of the standing pulse rate was 11; the average increase after exercise was 15, and the average time of the return of the pulse rate to the previous standing level was thirty seconds. The average change in blood pressure after standing two minutes was an increase of 7 mm. Hg. The average index of the group was 12.94.

TABLE III
EFFECT OF DIGITALIS ON NORMALS

	CONTROL SCORE	DIGITALIZED SCORE	AMOUNT DIGITALIS
1.	16	10	1.6 Gm.
2.	6	-3	1.4 Gm.
3.	14	13	1.2 Gm.
4.	16	16	1.3 Gm.
5.	16	15	1.2 Gm.
6.	16	9	1.3 Gm.
7.	10	8	1.5 Gm.
8.	14	9	1.2 Gm.
9.	15	7	1.2 Gm.
10.	14	16	1.6 Gm.

The Effect of Digitalis on the Index of Normal Controls.—The medical house officers were the subjects of this study. The test was done before and after digitalization (Table III). Digitalis was given in the following manner: Two doses of 0.5 Gm. of U.S.P. powder were given six hours apart, and 0.2 Gm. was given at intervals of six hours until nausea occurred. The index in the control observations was, with one exception, within the "fair" to "excellent" range. After digitalization the index was lower in eight instances, slightly higher in one case, and unchanged in one case. The reduction in the index was due to the slower return of the heart rate, after exercise, to the previous standing level. This (delay in the return of the pulse rate to the previous standing level after exercise) is in agreement with the observations of Parkinson⁸ in cases of soldiers' heart.

TABLE IV
HEART CONDITIONS
SUMMARY

CONDITION	NO.	AGE RANGE	SCORE RANGE	AVERAGE	STANDARD DEVIATION
Aortic insufficiency	2	37, 47	11, 16	13.5	2.5
Auricular fibrillation, idiopathic	2	35, 43	3, 13	8.0	5.0
Arteriosclerotic heart disease	13	41 to 78	4 to 15	9.92	3.647
Coronary thrombosis	16	33 to 59	6 to 16	10.63	3.016
Hypertensive heart disease	37	39 to 66	-1 to 16	9.81	4.05
Rheumatic heart disease	51	13 to 68	-3 to 17	10.1	4.736
Miscellaneous	5	19 to 72	4 to 13	9.2	3.2
Total	126	13 to 78	-3 to 17	10.05	4.24

The Schneider Test in Various Pathologic Conditions.—The test was performed on 121 patients with various diseases of the circulatory system, and on five patients with miscellaneous conditions. All of the

TABLE V
SCORES
CONTROLS CONTRASTED WITH HEART CASES

	CONTROLS		HEART CASES	
	NUMBER	PER CENT	NUMBER	PER CENT
Excellent (14-18)	34	24.6	29	23.0
Very good (11-13)	47	34.1	38	30.2
Fair (9-10)	22	15.9	18	14.3
Doubtful (7-8)	11	8.0	13	10.3
Unsatisfactory (below 7)	24	17.4	28	22.2
Total	138		126	

Comparison Of Normal Controls With Heart Cases.

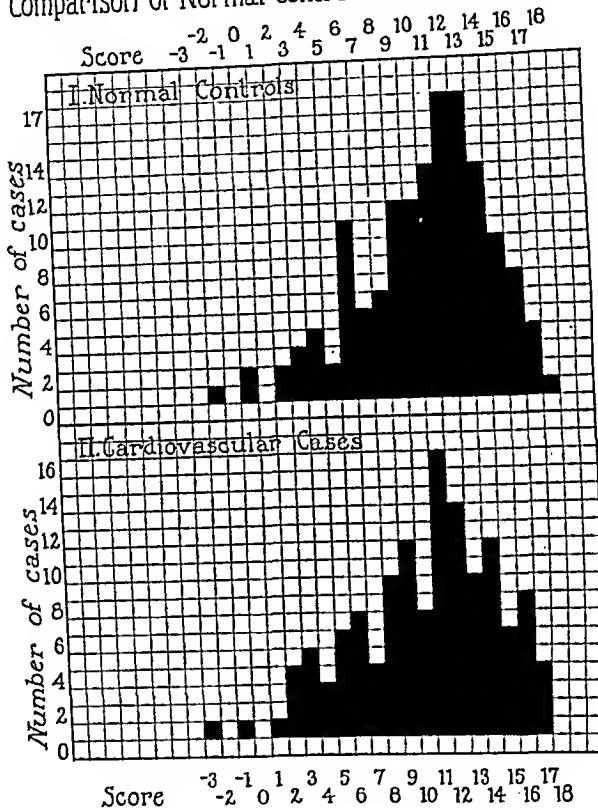


Fig. 1.

patients were in fair to good condition, and cardiac failure, when present, was mild. All of the patients were ambulatory and were attending either the outpatient department of the University Hospitals or the private consulting room of one of us. Table IV gives the data on the 126 patients. The score range was from minus 3 to 17, with an average index of 10.05. The variation of scores may be judged by the standard deviation of 4.24 and the standard error of 0.3784. The distribution of these pathologic cases is contrasted with that of the normal controls in Table V. There was a remarkable parallelism, and this is graphically illustrated in Fig. 1. The patients with all types of cardiovascular dis-

case behaved much the same as the large group of normals, although the normals skewed slightly to the right (slightly higher scores), and the abnormals skewed slightly to the left (slightly lower scores).

TABLE VI
HYPERTENSIVE CARDIOVASCULAR DISEASE

DISTRIBUTION OF SCORES	
NUMBER	SCORE
1	-1
3	3
2	4
1	5
1	6
2	8
5	9
3	10
5	11
5	12
2	13
4	14
3	16
Average	9.81
Standard deviation	4.05
Standard error	0.471

Hypertensive Cardiovascular Disease.—Thirty-seven patients with persistent hypertension were studied. The group included patients without heart failure, patients with moderate failure, and patients who were digitalized and not digitalized. The scores ranged from minus 1 to 16, with an average of 9.81. The failure group (all but one of whom were digitalized) ranged from 3 to 14, with an average of 10.0. The non-failure group scored from minus 1 to 16, with an average of 9.7. In other words, the average index in this group would be classed as “fair,” with many cases falling in the “very good” and “excellent” groups (Table VI).

TABLE VII
ARTERIOSCLEROTIC HEART DISEASE

CASE	SEX	AGE	FAILURE	DIGITALIZED	INDEX
1	M	47	0	0	8
2	M	58	0	0	12
3	M	56	+	+	11
4	M	78	0	0 A. F.	9
5	M	46	0	0	15
6	M	41	0	0	8
			Rt. B.B.B.		
7	M	44	0	0	12
8	M	53	0	+	4
9	F	55	0	+	6
10	F	60	0	+	14
11	M	65	0	0 A. F.	15
12	M	52	0	0	11
13	M	61	0	+	4
Range of scores				4 to 15	
Average				9.92	
Standard deviation				3.647	
Standard error				1.81	

Angina Pectoris and Myocardial Infarction.—Thirteen patients with coronary arteriosclerosis and angina pectoris were studied (Table VII). The indices ranged from 4 to 15, with an average of 9.92.

TABLE VIII
MYOCARDIAL INFARCTION

DISTRIBUTION OF SCORES	
NUMBER	SCORE
1	6
2	7
3	8
1	9
2	11
2	12
2	13
1	14
1	15
1	16
Range of scores	6 to 16
Average	10.63
Standard deviation	3.016

Sixteen cases of old myocardial infarction in relatively young men are summarized in Table VIII. The index ranged from 6 to 16, with an average of 10.63. Four patients whose illness dated back only three months gave good scores.

TABLE IX
RHEUMATIC HEART DISEASE

DISTRIBUTION OF SCORES	
NUMBER	SCORE
1	-3
1	1
2	2
1	3
5	5
4	6
2	7
1	8
3	9
4	10
6	11
3	12
3	13
5	14
3	15
3	16
4	17
Range of scores	-3 to 17
Average	10.1
Standard deviation	4.736
Standard error	0.464

Rheumatic Heart Disease.—Fifty-one patients with rheumatic heart disease and severe valve lesions were studied (Table IX). The index

ranged from minus 3 to 17, with an average of 10.1. The patients with cardiac failure had scores ranging from 3 to 17 (average, 11.8), and the patients without cardiac failure had scores ranging from minus 3 to 17, with an average of 9.8. Digitalis made no appreciable difference in the score. The patients with combined aortic and mitral disease did equally as well as the patients with mitral stenosis alone. Patients with normal sinus rhythm and those with auricular fibrillation did equally well. In this group of fifty-one patients, thirty-four had a "fair" to "excellent" rating.

Auricular Fibrillation, Etiology Unknown.—Two male patients, aged 35 and 43 years, respectively, had chronic auricular fibrillation without any discoverable cause. They were both active; the first was a physician, the second, a crane operator. Their scores were 3 and 13, respectively.

Normal Mechanism.—The cardiac mechanism was normal in ninety-four cases. The scores ranged from minus 3 to 17, with an average of 9.9 (Table X).

TABLE X
NORMAL MECHANISM

	NUMBER	RANGE	AVERAGE
Aortic insufficiency (syphilitic)	2	11, 16	13.5
Arteriosclerotic heart disease	11	4 to 15	9.5
Coronary thrombosis	15	6 to 16	10.5
Hypertensive heart disease	33	-1 to 16	9.6
Hypothyroidism	1	12	
Leucemia and anemia	1	9	
Right bundle branch block	1	13	
Rheumatic heart disease	30	-3 to 17	9.5
Total	94	-3 to 17	9.9

Auricular Fibrillation.—In thirty-two cases of auricular fibrillation the index variation was from 2 to 17, with an average of 11.9 (Table XI).

TABLE XI
AURICULAR FIBRILLATION

	NUMBER	RANGE	AVERAGE
Arteriosclerotic heart disease	2	9, 15	12.0
Congenital heart disease	1	8	
Coronary thrombosis	1	12	
Hypertensive heart disease	4	9 to 16	10.3
Hyperthyroidism	1	4	
Idiopathic	2	3, 13	8.0
Rheumatic heart disease	21	2 to 17	10.5
Total	32	2 to 17	11.9

Patients With No Heart Failure.—In 102 cases there were no signs of congestive failure. Here the scores ranged from 2 to 17, with an average of 10.1 in the digitalized group, and from minus 3 to 17, with an average of 10, in the undigitalized group (Table XII).

TABLE XII
PATIENTS WITH NO HEART FAILURE

	DIGITALIZED			NOT DIGITALIZED			TOTAL		
	NO.	RANGE	AV.	NO.	RANGE	AV.	NO.	RANGE	AV.
Aortic insufficiency (syphilitic)	1	16					1	16	
Arteriosclerotic heart disease	4	4 to 14	7.0	8	4 to 15	11.3	12	4 to 15	9.9
Auricular fibrillation (idiopathic)	2	3, 13	8.0				2	3, 13	8.0
Coronary thrombosis	2	6, 12	9.0	14	7 to 16	10.8	16	6 to 16	10.6
Hypertensive heart disease	2	9, 16	12.5	21	-1 to 16	9.4	23	-1 to 16	9.7
Hyperthyroidism; A. F.	1	4					1	4	
Hypothyroidism				1	12		1	12	
Leucemia and anemia				1	9		1	9	
Rheumatic heart disease	17	2 to 17	10.5	26	-3 to 17	9.3	43	-3 to 17	9.8
Right bundle branch block				1	13		1	13	
Tetralogy of Fallot; A. F.	1	8					1	8	
Total	30	2 to 17	10.1	72	-3 to 17	10	102	-3 to 17	10.0

Cardiac Failure.—There were twenty-three cases of mild congestive failure; all but one of these patients were digitalized. The index in the digitalized group ranged from 3 to 17, with an average of 12 (Table XIII).

TABLE XIII
CARDIAC FAILURE

	DIGITALIZED			NOT DIGITALIZED			TOTAL		
	NO.	RANGE	AV.	NO.	RANGE	AV.	NO.	RANGE	AV.
Aortic insufficiency (syphilitic)	1	11					1	11	
Arteriosclerotic heart disease	1	11					1	11	
Hypertensive heart disease	13	3 to 14	9.5	1	12		14	3 to 14	11.8
Rheumatic heart disease	8	3 to 17	11.8				8	3 to 17	10.0
Total	23	3 to 17	12.0	1	12		24	3 to 17	11.7

This study of 126 patients, 121 of whom had serious cardiac or hypertensive disease, frequently showed favorable Schneider indices. This emphasizes the contention of Schneider, Armstrong, and Scott that an unfavorable test alone must not disqualify, and, likewise, that a favorable result must be backed up with a careful history and physical examination. The Schneider index is frequently as favorable in persons with organic cardiovascular disease as in normal controls, and cannot be employed to differentiate normal from abnormal cardiovascular states. The limitations of the Schneider index have been emphasized. The test is most valuable for follow-up observations, for a lowering of the index signifies some variation in either the psychic or the physical condition.

CONCLUSIONS

1. As a test of physical efficiency of the cardiovascular system, the Schneider test makes very slight demand on the cardiovascular reserve.

2. The Schneider test is sensitive to both physical and psychic factors.
3. The Schneider index was obtained on ten digitalized normal controls. The index was lower in eight cases, unchanged in one case, and increased in one case. The reduction in the index was due to the slower return of the heart rate, after exercise, to the standing level.
4. Of 37 cases of hypertensive disease, the index was "excellent" in 7, "very good" in 12, "fair" in 8, and "doubtful" or "unsatisfactory" in 10.
5. In 13 cases of angina pectoris the indices ranged from "doubtful" to "very good."
6. Of 16 cases of remote myocardial infarction, the range was from "fair" to "excellent" in 10.
7. In 51 cases of rheumatic heart disease, 15 indices were "excellent," 12 were "very good," 7 were "fair," 3 were "doubtful," and 14 were "unsatisfactory."

We extend our thanks to Dr. Joseph Wearn for his stimulating interest in this study, and to the members of the resident medical staff of Lakeside Hospital who were the subjects of the digitalis experiments.

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ADDENDUM

Brouha and Heath recently published a paper (Brouha, Lucien, and Heath, Clark W.: Resting-Pulse and Blood Pressure Values in Relation to Physical Fitness in Young Men, *New England J. Med.* 228: 473, 1943) showing that there was no satisfactory relation between basal pulse rate, sitting pulse rate, and physical fitness for strenuous exertion in normal, healthy young men, and that emotional factors are largely responsible for the high resting pulse rates that are commonly found during the preinduction medical examination of healthy young men.

BLOOD PRESSURE IN THE AGED

A STUDY OF ONE THOUSAND ELDERLY MALE SUBJECTS

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THE realization that there are ever increasing numbers of aged persons in the United States has given fresh impetus to the study of geriatrics. In a period of forty years (1900-1940), during which the population of this country increased slightly more than one and one-half times, the number of persons 65 years old, or older, almost trebled (approximately 9,000,000). As this change in the age distribution of the population continues, the physician will be confronted more and more with the problem of the care of the aged and the diseases and infirmities arising from the senile state. For a clearer understanding of these problems, further study of the physiology and pathology of senescence and the establishment of normal standards for old age are essential.

Most statistics concerning the variations of blood pressure with age are based upon studies of comparatively young adults. In some series the number of senile subjects was too small to permit of accurate analysis of blood pressure trends in old age. In others, all elderly persons were classified as one homogeneous group under a designation such as "subjects over the age of 60," and no attempt was made to consider the respective age subdivisions of this group. Hence such studies contributed little to an understanding of the blood pressure changes in the latter decades of life.

The concept that blood pressure increases with the process of aging is so deeply rooted that the old formula "100 plus your age" is still universally applied by the laity, and is even today accepted by some physicians. That normal blood pressure does rise with advancing years, but much more slowly than the age, is suggested by the compilations of life insurance underwriters.^{1, 2} Their tables indicate that, normally, the blood pressure of white men rises from 120/79 at the age of 20 years to 138/89 at the age of 65 years.

Bowes,³ in a study of the average blood pressure of one hundred fifty aged subjects, observed a similar increase with advancing age. The systolic pressures of the men rose from 145 mm. in the 60- to 65-year-old group to 163 mm. in the 80- to 84-year-old group, and the pulse pressure increased from 63 mm. to 80 mm. in the same period.

Lewis,⁴ in an analysis of blood pressure variations, observed that the greatest rise in systolic pressure occurred after the age of 65 years.

From the U. S. Marine Hospital.
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His study, however, included only one hundred men, twenty in each decade from the age of 40 to 89 years. The average systolic pressure rose from 116 mm. in the 40- to 44-year-old group to 158 mm. in the 85- to 89-year-old group. The average diastolic pressure, on the other hand, showed little change in succeeding decades.

Miller's⁵ study of eight hundred fifty-three men and one hundred twenty-eight women who were past middle age also showed that there is a rise in average systolic pressure with advancing years. At 50 to 54 years in the male group, the systolic level was 132 mm., and rose to 157 mm. in the 85- to 89-year-old group. The pulse pressure showed a corresponding rise from 46 mm. to 71 mm., whereas the diastolic pressure varied only slightly in the same interval (84 mm. to 87 mm.).

Although such observations seem to indicate that systolic pressure normally tends to increase with age, not everyone agrees that this is true. Alvarez and Stanley⁶ have stated that a systolic pressure of 115 mm. is just as normal, and one of 140 mm. just as abnormal, for an old man as a young one. Similar views as to the constancy of normal blood pressure were expressed by Huber,⁷ Faught,⁸ and others.

Robinson and Brueer⁹ have declared even more emphatically that the range of normal blood pressure must be considered "as immutable and as constant as the temperature and pulse rate." They point out that the average levels which were regarded as normal in previous studies were distorted by including abnormally high pressures. The authors maintain that, although elevated pressures rise with advancing years, normal levels remain unchanged. In their opinion, normal blood pressure does not exceed 120 mm., and levels of 130 mm. to 140 mm. can never be considered normal at any age. In their statistical study of more than ten thousand persons, the authors attempted to eliminate the abnormal pressures in order to arrive at a more accurate average of normal blood pressure. This was supposed to be accomplished by excluding subjects with a pressure in excess of 140/90, because, with this level as the upper limit of normal, the authors found no increase with age. As pointed out by Treloar,¹⁰ this manipulation was actually a means of forcing a desired result. Although only 13.3 per cent of their male subjects were excluded by this procedure, it will be shown that, when aged subjects are taken at random, over 60 per cent would be affected by such a procedure. It is further to be noted that although 7,478 men were included in their entire group, only 189 were more than 65 years of age. Finally, the authors state that 120 mm., systolic, and 80 mm., diastolic, are the upper limits of normal blood pressure, and maintain that when these levels are exceeded there is an abrupt rise in death rate. That this does not hold for certain elderly persons who comprised an appreciable percentage of the entire group will be shown in this study.

It is evident, therefore, that little accurate information is available concerning blood pressure trends among persons over the age of 60 years. Furthermore, no attempt has previously been made to classify such subjects into blood pressure groups (normal, systolic hypertension, diastolic hypertension) and to study the incidence of each group in old age. It is realized that differentiation on the basis of blood pressure levels alone is purely arbitrary, but the value of such a classification, when it is correlated with life expectancy studies for the respective groups, is apparent.

For the purpose of this study an analysis was made of the blood pressure levels of one thousand male subjects, all of whom were retired seamen between the ages of 60 and 95 years. The age distribution of the group was fairly uniform throughout this period. The mariners were residents of Sailors Snug Harbor, an institution open to seafaring men who lack financial support, are unemployed because of the infirmities of old age, or are incapacitated by disease or injury. The majority of these men were of Scandinavian descent. Their social habits had been relatively uniform; almost all of them had used alcohol moderately or in excess. Most of the subjects had been exposed to diseases that are prevalent all over the earth. The nature of their former occupation and recreation differed sharply from that of the sedentary urban groups who have been analyzed in other studies. Inasmuch as these men may be regarded as of a relatively "pure strain" with respect to racial and environmental factors, and were otherwise unselected, they seemed ideal for a study of the relationship between arterial pressure and life expectancy.

The measurements were made during routine morning rounds, with a mercury manometer, by the auscultatory method. The level at the beginning of the fourth phase was taken as the diastolic pressure. Emotional factors were minimal, and the subjects were accustomed to having their blood pressure measured.

RESULTS

Table I shows the effect of age upon average blood pressure. The systolic rose from 147 mm. in the 60- to 64-year-old group to 160 mm. in the 85- to 95-year-old group. The pulse pressure increased from 65 mm. to 74 mm. over the same period. The diastolic pressure varied little after the age of 65 years.

TABLE I
AVERAGE BLOOD PRESSURE IN OLD AGE

AGE (YEARS)	NUMBER	SYSTOLIC	DIASTOLIC	PULSE PRESSURE
60-64	120	147	82	65
65-69	201	153	86	67
70-74	157	154	85	69
75-79	248	156	86	70
80-84	170	157	85	72
85-95	104	160	86	74

Table II shows the relation between age and blood pressure levels. All blood pressures below 150/95 were classified as *normal*; when the systolic and diastolic levels exceeded 150/95, *diastolic hypertension* was said to be present, whereas systolic pressures above 150 mm. with diastolic pressures under 95 mm. were regarded as indicative of *systolic hypertension*. It is seen that the percentage of "normals" decreased from 67 per cent in the 60- to 64-year-old group to 34 per cent in the 85- to 95-year-old group. Of the one thousand subjects, slightly less than half had blood pressures of 150/95 or less. The incidence of systolic hypertension rose progressively with age from 17 per cent to 38 per cent, and, of the entire group, more than one-quarter had this type of blood pressure elevation. On the other hand, the incidence of diastolic hypertension seemed to rise more slowly with age (16 per cent to 28 per cent), and those who manifested it comprised less than one-quarter of the entire group. Of the one thousand subjects, therefore, it can be said that approximately two in four were "normals," one in four had "systolic hypertension," and one in four had "diastolic hypertension." Actually, however, the commonest type of blood pressure elevation was systolic hypertension; it was present in more than one-third of all the subjects over the age of 75 years.

TABLE II

PERCENTAGE INCIDENCE OF NORMAL AND HIGH BLOOD PRESSURE LEVELS IN THE AGED
(1,000 SUBJECTS)

AGE (YEARS)	60-64 (120)	65-69 (201)	70-74 (157)	75-79 (248)	80-84 (170)	85-95 (104)	60-95 (1,000)
NORMAL (496)	67	54	52	39	40	34	49.6
SYSTOLIC HYPERTENSION (276)	17	24	26	36	38	38	27.6
DIASTOLIC HYPERTENSION (228)	16	22	22	25	22	28	22.8

In Table III an analysis is made of the variations in "normal" blood pressure with age. It is seen that in the four hundred and ninety-six subjects in this class the average normal systolic pressure rose from 132 mm. in the 60- to 69-year-old group to 136 mm. in the 80- to 95-year-old group. It has been stated by others that this rise is not the result of changes in normal pressure (120 mm. or less), but shows that prehypertensive levels were included in the normal group. Nevertheless, in this study, the incidence of normal pressure (in the restricted sense) decreased with age, whereas the incidence of upper levels of normal showed a corresponding rise. This strongly suggests that, among elderly persons, all levels of normal systolic pressure tend to increase with advancing years. In sharp contrast, the average normal diastolic pressure decreased slightly with age, and the incidence of

low diastolic pressures increased concomitantly. The cause for these changes in normal pressure will be discussed under systolic hypertension.

TABLE III
ANALYSIS OF TRENDS IN NORMAL GROUP
(496 SUBJECTS)

AGE (YEARS)	SYSTOLIC				DIASTOLIC			PULSE PRES- SURE
	AVER- AGE (MM.)	110 OR LESS	120 OR LESS	140-150	AVER- AGE (MM.)	70 OR LESS	90-95	
60-69	132	11%	30%	22%	78.3	35%	11%	51
70-79	134	8%	26%	30%	77.1	44%	12%	57
80-95	136	4%	20%	34%	76.0	48%	12%	60

On the assumption that the subjects of this study were a representative sample of the many who preceded them at Sailors Snug Harbor, an analysis of three hundred sixty-two consecutive deaths was undertaken, and the cases were classified according to blood pressure levels and age at death. By comparing the incidence of the various levels of blood pressure in the living with that of the same levels among those who had died, it was possible to relate expected and actual mortality (Table IV).

TABLE IV
LIFE EXPECTANCY IN THE AGED*

AGE	60-64	65-69	70-74	75-79	80-84	85-95	60-95
NORMAL	-10	-10	-15	-10	- 7	- 6	-10
SYSTOLIC HYPERTENSION	-18	- 8	0	- 6	- 3	-13	- 7
DIASTOLIC HYPERTENSION	+62	+36	+36	+24	+20	+25	+32

*Percentage variation from unexpected mortality.

DISCUSSION

Considerable interest has been aroused by the contention of Robinson and Bruce⁹ that systolic pressure in excess of 120 mm. is "in the zone of hypertension," and that anything above this level is attended by an abrupt rise in mortality rate. Although this index of prognosis may be accurate for younger adults, the clinician has long been aware of its inadequacy in predicting life expectancy in the aged. As pointed out by Fineberg,¹¹ elevation of the systolic pressure, with a normal or low diastolic pressure, is found among aged persons who are comparatively free from the signs and symptoms of cardiovascular disease. The fact that this form of hypertension does not influence the health or life expectancy of the patient was commented upon more recently by Boas.¹² In this study it has been shown that such subjects make up a large percentage of the older groups. Previously, the idea that this type of blood pressure elevation is benign was based merely on

clinical impression, but additional support is furnished by the analysis in Table IV. The latter expresses actual mortality for the respective age-blood pressure groups in terms of percentage variation from expected mortality. The figures are based on the ratio of actual to expected deaths in each group. The expected mortality was derived from the incidence of the various blood pressure levels in the living subjects. The actual mortality was calculated from an analysis of three hundred sixty-two consecutive deaths prior to 1940. Comparison of these figures is believed justified in view of the uniformity of the groups under consideration. It is clear that the life expectancy of the subjects with systolic hypertension is strikingly similar to that of the subjects with normal blood pressure, but the prognosis of diastolic hypertension is very different. Consequently, life expectancy in the aged would seem to be definitely related to the diastolic blood pressure, rather than to the systolic.

Systolic hypertension in old age is commonly regarded as a consequence of diminished elasticity of the aorta and its large branches, and is usually associated with marked arteriosclerosis of these vessels.¹³ As a result of loss of distensibility of the vessel wall, the arterial pressure becomes elevated above normal with each ventricular systole. At the same time, diminution in the elastic recoil of the aorta tends to produce a lowering of the diastolic pressure, with a further increase in the pulse pressure. This effect in some instances is counterbalanced by the widening and elongation of the aorta which are frequently observed in old age. Wiggers¹⁴ is of the opinion that, in some cases, systolic hypertension may actually represent long-standing diastolic hypertension complicated by sclerosis and rigidity of the aorta. In fact, when the heart is enlarged it is generally impossible to exclude the possibility that diastolic hypertension may have been present previously in these aged subjects. On the other hand, the frequent association of a small heart and marked arteriosclerosis of the aorta, as well as the much more favorable life expectancy in this group, strongly suggests that systolic hypertension in most instances originates as such, and has its own distinct mechanism. Fahr and Davis,¹⁵ furthermore, have shown that increased rigidity of the arterial system, without an associated decrease in internal diameter, does not impose an added burden upon the heart.

It is worthy of emphasis that "normal" systolic pressure increased with age, whereas "normal" diastolic pressure showed a tendency to fall. The alteration in blood pressure produced by arteriosclerosis, therefore, is manifested not only by an increased incidence of systolic hypertension with age, but also by changes in pulse pressure even in normal persons (Table III). Robinson and Bruecr⁹ admitted that they were unable to explain the rise in blood pressure that occurred with age in 10 per cent of subjects whose systolic levels were less than 120

mm. Study of the elderly subjects at Sailors Snug Harbor revealed an increase in "normal" systolic pressure with age, regardless of whether the upper limit of normal was taken as 150 mm. or any level below this figure. This rise in pressure was considerably less, however, than that for the group as a whole, obviously because in the latter there was an increasing incidence of hypertension with advancing age.

Robinson and Brucer⁹ excluded from their study all patients with systolic blood pressures above 140 mm. They originally considered this as the upper limit of normal mainly because average blood pressure did not increase with age when higher levels were discarded. This eliminated only 13.3 per cent of their entire group, which included subjects from 15 to more than 80 years of age. As already mentioned, the number of elderly subjects in their series was relatively small. If such a procedure were applied to this study, in which all of the subjects were over sixty years of age, 64 per cent of the entire group would have been eliminated. A similar percentage would have been involved in the old age groups studied by Miller⁵ and Willis.¹⁶ Furthermore, if Robinson and Brucer's revised definition of normal blood pressure (120 mm. or less) were applied to these aged seamen, only 13 per cent of the entire group could qualify as normal!

In the light of present knowledge, it is impossible to accurately state at what level physiologic pressures merge into pathologic ones. If by normal pressure one means levels consistently compatible with a long and healthy life, then so-called systolic hypertension in the aged should be included in this category. In the elderly patient with a blood pressure of about 170/70, with no cardiac enlargement or other manifestations of cardiovascular disease, the combination of elevated systolic pressure and low diastolic pressure may be regarded as physiologic. Although there is increasing evidence that arteriosclerosis is a disease rather than a degenerative change, it cannot be denied that the process of aging may leave its mark upon the vessels as well as the hair, skin, skeleton, and other structures. The repeated stretching and recoil of the arterial wall and the inherent tendency for elastic tissue to deteriorate with age may be the factors which underlie systolic hypertension. At any rate, it is far more accurate to regard the latter as "normal" than to identify it with diastolic hypertension, as insurance statistics inadvertently have done.

Although it is suggested that a relatively high systolic pressure may be regarded as physiologic in old age, the reverse holds true for diastolic pressure. Although 64 per cent of the entire group had systolic pressures above 140 mm., only 30 per cent had diastolic pressures in excess of 90 mm. In the "normal" group the average diastolic pressure was only 77 mm. The average diastolic pressure for normals and systolic hypertensives combined (77.2 per cent of the entire group) was 78 mm. The average diastolic pressure for all the subjects was

85 mm. These data seem to support the view of Robinson and Brucer⁹ that the upper level of normal diastolic pressure has in the past been set too high.

This study has dealt with the arteriosclerotic type of systolic hypertension. Among other causes for elevation of the systolic pressure, with normal or low diastolic levels, are hyperthyroidism, aortic insufficiency, and heart block. The latter conditions are obviously associated with increased mortality rates, so that their inclusion in a study of the arteriosclerotic type would greatly alter the life expectancy figures for this group. The fact that other studies have not made this differentiation may explain the poor prognosis often given to this form of hypertension.

SUMMARY AND CONCLUSIONS

A statistical analysis of the blood pressure levels of one thousand male subjects, all retired seamen between the ages of 60 and 95 years, is presented. The variations in blood pressure and the inferences drawn therefrom are as follows:

1. Average systolic pressure and pulse pressure increase appreciably with age, whereas average diastolic pressure shows little variation after the age of 65 years.
2. The incidence of "normal" blood pressure (150/95 or less) falls markedly with age. Less than half of the subjects fell in this group.
3. Normal systolic pressure shows an increase with age, regardless of whether the upper limit is set at 150 mm. or at any figure below this level. All levels within the range of normal seem to participate in this change.
4. Normal diastolic pressure shows a tendency to fall with age, and the number of subjects with low diastolic pressures (70 mm. or less) increases correspondingly.
5. Arteriosclerosis not only increases the incidence of systolic hypertension with age, but also produces an increase in pulse pressure among subjects with normal blood pressure.
6. More than one-quarter of all the subjects and more than one-third of those over the age of 75 years had systolic hypertension.
7. A study of the ratio of actual to expected mortality revealed that the life expectancy of those with systolic hypertension was of the same order as for those with normal pressure. Diastolic hypertension, on the other hand, carries a much more unfavorable prognosis.
8. The life expectancy in this group was related to the diastolic, rather than to the systolic, pressure.
9. The incidence of diastolic hypertension increases more slowly with age; it was found in less than one-quarter of the entire group.
10. Normal diastolic pressure, as well as average diastolic pressure, was comparatively low, and it would seem that the upper limit of normal has in the past been set at too high a level.

11. The clinical course and life expectancy of patients with systolic hypertension strongly suggest that the latter originates as such, and has its own distinct mechanism.

12. For practical purposes, the clinician may regard systolic hypertension in the aged as "normal." Future study of the nature of atherosclerosis may reveal that it is physiologic in old age.

13. Finally, if 120 mm. represents the "true" upper limit of normal at any age, only 13 per cent of this group could be classified as normal.

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THE COMBINED USE OF STROPHANTHIN-K AND DIGITALIS IN THE TREATMENT OF CONGESTIVE HEART FAILURE

A PRELIMINARY REPORT

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THIS study was undertaken to ascertain the effects of the combined use of strophanthin-k and digitalis on patients with congestive heart failure, and to demonstrate the degree of effectiveness and safety of this treatment. Brams, et al.,¹ working with strophanthin alone, demonstrated that it was safe, and obtained therapeutic effects comparable to those of digitalis. The proper method of digitalization after the administration of strophanthin-k has never been satisfactorily established. Batterman, et al.,² combined the use of ouabain, which is closely allied to strophanthin-k, and digitalis, and gave six to eight cent units initially, followed by a maintenance dose. Preliminary observations convinced us that full digitalization was necessary to effect a maximum response. Consequently, the patients in this series were completely digitalized after the initial dose of strophanthin.

Strophanthin-k is a relatively new therapeutic agent, and is not to be confused with strophanthin-g, or ouabain. Strophanthin-k is an amorphous glycoside derived from *Strophanthus kombé*; strophanthin-g is a crystalline glycoside derived from *Strophanthus gratus*. The crystalline strophanthins have greater toxicity and, consequently, a smaller therapeutic range than the amorphous strophanthins.

When strophanthin-k is given intravenously it acts within a few minutes, and is almost wholly excreted within twenty-four hours. Digitalis, on the other hand, is slow in action, and its rate of absorption and excretion is prolonged. These properties of the two drugs constitute the rationale of their combined use, for, as the action of strophanthin begins to wane, the digitalis begins to exert its maximum effect, and becomes the cardinal therapeutic agent.

The cases selected for study included patients with acute or chronic heart failure, irrespective of cause, who had not previously received digitalis for a period of at least ten days. The symptomatic and supportive care was uniform, and consisted of rest in bed, sedatives, oxygen, ammonium chloride, and a soft, salt-free diet. In addition to clinical evidence of failure, the exact cardiac status was ascertained by measurement of the venous pressure and the recording of electrocardiograms

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TABLE I

PATIENT	DIAG.	AGE	RACE	SEX	INITIAL RATE AND RHYTHM	FINAL RATE AND RHYTHM	INIT. TAL. V.P.	FINAL V.P.	INT. TAL. C.T.	FUSAL C.T.	TOTAL STROPH. (MMG.)	TOTAL DIGI- TALIS (C.T.)	COMPE- SATION		RESULTS AND REMARKS
													BT.	LT.	
J. A.	ASHD HHD	56	C	F	165 (F)	94 (F)	27	10	--	--	0.25	19	3	4	Died in uremia. Had fully com- pensated
E. B.	ASHD	76	C	M	93 (F)	68 (F)	31	7	--	--	0.25	20	3	4	Discharged fully compensated
A. G.	ASHD	46	W	M	115 (F)	75 (R)	28	7.5	32	--	0.25	18	2	5	Discharged fully compensated
R. H.	HHD	63	W	M	102	88	13	7.5	25	--	0.25	23	1	4	Discharged fully compensated
M. J.	SHD	38	C	M	103	88	20	--	22	--	0.25	--	--	--	Failed to compensate. Aortic aneurysm compressing pul- monary artery
O. M.	ASHD	70	C	M	170 (F)	82 (F)	--	10.5	--	--	0.25	20	3	13	Discharged fully compensated
A. M.	THD	38	C	F	112	71	23	1.5	--	--	0.25	13	2	5	Discharged fully compensated
E. P.	HHD	33	W	F	102	86	21	10.5	--	--	0.25	14	3	5	Discharged fully compensated
W. T.	ASHD	53	C	M	112	--	--	--	--	--	0.25	--	--	--	Died. Coronary occlusion, femo- ral and cerebral emboli
O. W.	ASHD	71	C	M	88	72	21	10	--	--	0.25	22	3	6	Discharged fully compensated
D. R.	ASHD HHD	68	C	M	96 (F)	72 (F)	22	6	15	--	0.25	16	3	5	Discharged fully compensated
N. T.	HHD	42	C	F	126	96	27	8.5	32	11	0.25	20	3	3	Discharged fully compensated
C. T.	SHD	27	C	M	103	80	30	8	32	17	0.25	24	6	8	Discharged fully compensated
C. T.	SHD	27	C	M	106	75	25	10.5	30	14	0.25	12	3	3	Discharged fully compensated
E. W.	ASHD HHD	62	C	F	87 (F)	81 (F)	25	10.5	22	17	0.25	20	3	3	Discharged fully compensated
G. C.	ASHD HHD	68	C	M	75	75	27	13.5	30	15	0.25	21	4	1	Discharged fully compensated
M. W.	ASHD	58	C	M	106	70	29	10.5	34	18	0.25	24	6	16	Discharged fully compensated
R. M.	ASHD HHD	74	C	M	93	78	22	7	12	11	0.25	12	2	2	Discharged fully compensated

F=auricular fibrillation; R=normal rhythm; V.P.=ventricular pressure; C.T.=circulation time; C.M.=cent. med.; ASHD=arteriosclerotic heart disease; HHD=hypertensive heart disease; SHD=sphygmia; heart affec. co.; THD=thyrotoxic heart affec. co.

in all cases. Deeholin circulation time measurements also were obtained in the last seven cases; they were made before, and at daily intervals after, the institution of treatment.

Once the cardiac status was known, the patient was given, intravenously, 0.25 mg. of strophanthin-k, diluted with 10 c.c. of physiologic saline, over a period of three minutes. Slow administration was employed in order to allow complete fixation of the drug by the myocardium. Immediately, six to nine grains of digitalis leaf were given orally, followed by three grains three times a day until the patient was digitalized. A close record was kept of subjective improvement and signs of toxicity.

The criteria of recovery from heart failure consisted of disappearance of dyspnea, râles, cyanosis, and edema, diminution in the size of the liver, and return of the venous pressure and circulation time to normal. Electrocardiograms, which were taken daily, offered objective evidence as to the effect on the myocardium and conduction mechanism.

Eighteen patients were studied, fifteen of whom were completely relieved of their heart failure. Two of the patients died, one of uremia, and the other of peripheral and cerebral emboli eight days after coronary occlusion. Both of these patients, however, had recovered from heart failure prior to death. One patient with an aortic aneurysm compressing the pulmonary artery failed to respond.

Fifteen of the patients were colored and three were white; thirteen were males and five were females. The ages ranged from 27 to 76 years, averaging 53.8 years. There were six cases of pure arteriosclerotic heart disease, three of hypertensive heart disease, five of combined hypertensive and arteriosclerotic heart disease, three of syphilitic heart disease, and one of thyrotoxic heart disease.

The average time required for the right side of the heart to compensate was 3.1 days, and, for complete compensation, 5.5 days.

The total amount of strophanthin-k given to each patient was 0.25 mg.; the total amount of digitalis required for digitalizing each patient ranged from 12 to 24 cat units, averaging 18.5 cat units.

All patients noticed subjective improvement within the first two to six hours; this was progressive, and closely paralleled objective signs of improved cardiac function. There were practically no untoward toxic manifestations, aside from the nausea and occasional vomiting associated with full digitalization. Electrocardiograms failed to show any detrimental effects on the conduction mechanism or on the state of the myocardium.

The heart rate was not strikingly altered during the first six to twelve hours, although there was a uniform and progressive slowing of the pulse rate. The rhythm remained unchanged in all cases of sinus rhythm. Six patients had auricular fibrillation, one of whom recovered normal rhythm; this patient's auricular fibrillation had been present for two

months, and followed thyroidectomy. The absence of definite and more immediate bradycardia suggests the possible necessity of giving a larger initial dose of strophanthin-k.

The rapidity of recovery, particularly of the right side of the heart, was the most striking and dramatic feature. Both clinical and objective observations demonstrated the effectiveness of the combined use of strophanthin-k and digitalis in this respect. It is our belief that full digitalization after giving strophanthin played a major role in effecting this rapid result.

CONCLUSIONS

1. The use of strophanthin-k and digitalis in combination is safe and efficient.
2. Full digitalization after giving strophanthin is essential.
3. Patients with congestive heart failure usually recover rapidly when this form of therapy is used.

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AORTIC REGURGITATION CAUSED BY DILATATION OF THE AORTIC ORIFICE AND ASSOCIATED WITH A CHARACTERISTIC VALVULAR LESION

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THERE are occasional references to aortic regurgitation unaccompanied by structural changes in the aortic valve leaflets.¹ It is known as "functional" aortic insufficiency, and is generally attributed to dilatation of the aortic ring. Arteriosclerosis,² hypertension,³ and chronic nephritis⁴ have been regarded as important factors in the pathogenesis of this type of aortic valvular insufficiency. The subject, which has always been controversial, received greater attention in previous years than it does at present. Nevertheless, Garvin⁵ recently reported fourteen instances of this unusual cardiac condition in a series of two hundred hypertensive patients.

There are cases of aortic regurgitation which are not easily classified because of certain clinical peculiarities. We refer to patients over the age of 50 years, usually near or past 60 years, and usually men, in whom the evidence for syphilitic infection is slight or nonexistent. Neither the history nor the physical examination indicates the presence of subacute bacterial endocarditis. Predominant aortic regurgitation of rheumatic origin is, of course, rare at this age, and can usually be excluded after brief consideration. The diastolic aortic murmur may or may not be transmitted down along the left sternal border, as in all types of aortic regurgitation, but in these elderly patients the transmission is frequently limited over a small area, in spite of the prominence of the murmur. The murmur may be loud and harsh, and is often fused with, or engrafted upon, an accentuated aortic second sound. Its physiologic significance may be questioned because the blood pressure changes and peripheral signs characteristic of aortic regurgitation are usually only moderately developed, and sometimes barely detectable. The systolic pressure in some cases is high enough (200 mm., or more) to indicate the existence of hypertension. The diastolic pressure is often higher than in the ordinary types of aortic regurgitation, occasionally ranging as high as 100 mm. It seldom falls below 50 mm.; so-called zero diastolic readings are rarely, if ever, recorded. A Corrigan pulse is present, but generally it is not as striking as in cases of well-developed aortic regurgitation of infectious origin. The other classical signs of aortic regurgitation are usually absent. We have not encountered a capillary pulse, a Duroziez murmur, or a Traube pistol shot sound.*

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*We have no experience in eliciting Loewenberg's⁶ sign of functional aortic valvular insufficiency, namely, the absence of a much higher systolic blood pressure in the legs than in the arms.

In six of the eleven cases on which this report is based the diastolic murmur was preceded by a short systolic aortic murmur, and, in one instance, there was a systolic thrill in the aortic area. The diastolic murmur was the striking physical sign in all cases.

Our interest in so-called functional aortic regurgitation was aroused by (1) our observation of elderly patients who appeared to have aortic regurgitation which we hesitated to designate as syphilitic because of their repeatedly negative blood Wassermann and Kahn reactions, and (2) by our observation at necropsy, in such cases, of changes in the aortic leaflets which were different from the ordinary lesions of syphilis, rheumatic fever, and atherosclerosis.



Fig. 1.—Case 2. Various types of central, free-marginal sclerosis, enlargement of the sinuses of Valsalva, dilatation of the aortic ring, and widening of the commissures by separation of the leaflets, in an aged, hypertensive patient with non-syphilitic aortic regurgitation. Note irregular thickening and lipping of the endocardium in the mid-portion of the posterior (middle) leaflet. The posterior sinus is enlarged. The right anterior sinus (*R*) is ballooned by cotton; the corpus arantii of the right leaflet has disappeared; the mid-portion of the free margin of the leaflet shows a crescentic indentation and is indurated; the process is terminated on each side by a bicornate sclerotic projection (small arrows). The left anterior leaflet shows a small, central, rodlike thickening of the free margin, 0.8 cm. long. The lateral portions of all leaflets are normally delicate, but somewhat elongated. They have been stretched apart, leaving a furrow at the third commissure (*X*). There is no calcium or atheroma in this aortic valve and scarcely any atheromatosis in the aortic arch.

This lesion is a sclerotic thickening confined to the mid-portion of the free edge of the aortic leaflets. It is essentially a loss and a fibrous replacement of the original corpora arantii, without involvement of the lateral portions of the free margin of the leaflet or of the body of the leaflet, except insofar as marked central involvement necessarily extends some distance toward the periphery. In some instances, the sclerotic thickening may extend from the mid-point almost throughout the entire length of the free edge of the leaflet. The commissures are not involved, except occasionally in a peculiar way, as indicated later.

This lesion in the mid-portion of the free margins may assume odd shapes and attain considerable size. All three leaflets are usually involved. The central thickening may appear as a bicornate projection, with two sclerotic tips or nodules enclosing a central sector where the valvular substance has been eroded (Fig. 2). The lesion is firm, densely sclerotic, and without resemblance either to the original corpus arantii or to verrucae. In some cases there is a rolled thickening or lipping of the free margin, most pronounced at the mid-point, and gradually tapering off into the delicate normal structure at the lateral portions of the leaflets (Fig. 4). The bicornate and the lipped progressions are the common types of deformity. Rarely, central lipping progresses to eversion of an entire leaflet, as in the "hinge valve" lesions of aortic insufficiency.^{7, 8} Also rarely, there is a buttonlike thickening or a shield formation over the site of the original corpus arantii. In some cases the three leaflets show different deformities; one may have central hornlike projections, the others be lipped or rolled in varying degree.



Fig. 2.—Case 4. The "bicornate" sclerotic lesions replace the corpora arantii of the aortic leaflets. Syphilitic aortitis is present, but does not involve the commissures. The lateral portions of all three leaflets remain normally delicate. Cotton partially balloons out the sinuses.

The hard, often calcific, roughening of the corpora arantii in the hypertrophied hearts of elderly men who had systolic aortic murmurs suggestive of aortic stenosis should not be confused with the central deformity of the leaflets herein described.

The central, free marginal fibrosis is one of a trio of changes characteristic of "functional" aortic regurgitation. The others are dilatation of the aortic ring, and enlargement in length and depth of the sinuses of Valsalva, with corresponding elongation of the aortic leaflets.

In most instances, as was pointed out by Osler,² the aortic ring is dilated; in our cases its circumference ranged from 7.5 to 10.5 cm.* In

*Osler's criteria require slight revision in the light of modern necropsy observation, as indicated by Roessle and Roulet.⁹

two of our eleven cases this could not be definitely established, for the circumference of the ring did not exceed 7.5 cm. However, dilatation of the root of the aorta, including the sinus area, was present in all eleven cases. Although, in most instances, this was merely continuous with the dilatation of the aortic ring, it sometimes was strikingly abrupt, i.e., the proximal portion of the ascending arch was engaged in a sacular, onion-shaped dilatation, resembling an aneurysm. Of course, no aneurysm in the true pathologic sense was present. With this supra-valvular dilatation, the aortic sinuses were enlarged and the aortic commissures were drawn outward, so that they were located on an aortic circumference as much as 4 or 5 cm. in excess of the aortic ring circumference. This was the situation in the two cases in which the aortic ring circumference was considered to be within normal limits; the aortic leaflets were elongated to cover the enlarged aortic lumen. Eventually they became incompetent.



Fig. 3.—Case 4. Same as Fig. 2, but enlarged to show more clearly the normal commissures and the bicornate lesions. Half of the left anterior leaflet, its sinus, and the adjacent aorta have been cut away. Commissure 3 is also missing.

It was clear, therefore, that aortic insufficiency existed in the entire group; in most instances it was secondary to dilatation of the aortic valvular ring, but occasionally to supra-valvular aortic dilatation that involved the sinuses. In view of this, and in the absence of typical valvular lesions of rheumatic and syphilitic heart disease, we tentatively spoke of this type of aortic insufficiency as "mechanical regurgitation."

As mentioned above, the sclerotic thickening of the valve leaflet did not extend into the commissures. However, we noted in some cases that the commissural junction, which normally is little more than a point

reached by the two adjacent portions of adjoining leaflets, was widened, not by fibrosis and edematous swelling, as is so often the case in syphilitic valvulitis, but by a pulling apart of the adjoining margins of the leaflets. The free margins in their lateral portions remained normally sharp-edged and appeared, if anything, lengthened, but the commissural junction became an actual space 2 or 3 mm. wide; it consisted of a depression without scarring, and resembled a furrow created by the tearing of normal attachments (Fig. 1). When this situation existed, there was an associated valvular insufficiency of marked degree.



Fig. 4.—Case 3. Central thickening along the free margins of the aortic leaflets, with normal commissures. No evidence of syphilis. Close inspection (aided by hand lens) of the right anterior leaflet (*R*) reveals early notching of the central, free-marginal lesion. The posterior (middle) leaflet shows more extensive sclerotic flapping of the free margin. Note slight degree of arteriosclerosis in the aorta.

The central marginal lesions occasionally occur in aortic leaflets which are the seat of lateral fenestrations. These fenestrations ordinarily do not cause aortic regurgitation, for they are above and beyond the line of closure of the leaflets. Rare exceptions have been recorded, but without unusual valvular lesions.^{3, 10} We have seen, at necropsy, definite fibrous central thickening of the leaflets (Fig. 5); the thickening extended laterally along the lower border of the fenestration. The aortic ring in such a case is markedly dilated.

“Mechanical regurgitation” and syphilis are not infrequently associated. Some hypertensive patients with moderate aortic regurgitation, similar clinically to the type herein discussed, have a positive blood Wassermann reaction. The valvular insufficiency may remain surprisingly stationary or sometimes be intermittent, thus presenting an interesting problem. Hypertension might be expected to accelerate the rapid course of syphilitic aortic regurgitation.

We have seen patients with aortic regurgitation who at necropsy had syphilitic aortitis, but did not have the classic lesion of syphilitic aortic regurgitation, namely, widening and scarring of the valvular commissures. In some cases "commissuritis" was entirely absent, and, in others, so slight as to be insignificant. The leaflets did not show the characteristic shrinkage and retraction. The only obvious valvular lesion associated with the regurgitation was a sclerotic, bicornate thickening or lipping of the mid-portion of the free margins of the leaflets. Regardless of whether this was prominent or only moderately developed, the aortic ring was dilated and the sinuses were enlarged.



Fig. 5.—This case is not included in the series herein reported because of the obvious extension of syphilitic aortitis into two of the commissures, A and C. Commissure B is also widened, but stretching by dilatation of the aortic ring may have been a factor. The lateral portions of each leaflet are delicate, showing no marginal extension of sclerosis. The lateral fenestrations remain unchanged. The central portion of each leaflet is thickened; the corpora arantii are replaced by (1) a shield in the right anterior and the posterior leaflets, and (2) a bicornate lesion in the left anterior leaflet. The aortic ring is widened (circumference, 10.0 cm.), and there is even greater widening of the root of the aorta. From a case of syphilitic heart disease, with inconstant aortic regurgitation; the murmur disappeared and reappeared over a period of six years.

Three of our eleven patients had positive blood Wassermann reactions. At necropsy, two of these had syphilitic aortitis without commissural lesions. The third patient showed no gross evidence of aortitis or commissural involvement. Other cases have not been included in our series because there was undoubted extension of the syphilitic process into one, or possibly two, commissures. However, the dilatation of the aortic ring and the characteristic central marginal lesions were so outstanding as to indicate that, even with commissural thickening, the aortic regurgitation was the result of more than one factor (see Fig. 5).

Although aortic regurgitation which is associated with a positive Wassermann reaction must nearly always be considered syphilitic, it is apparent that, in occasional cases, the pathologic process is not typical. This probably accounts for the prolonged and atypical clinical course exhibited by some patients.

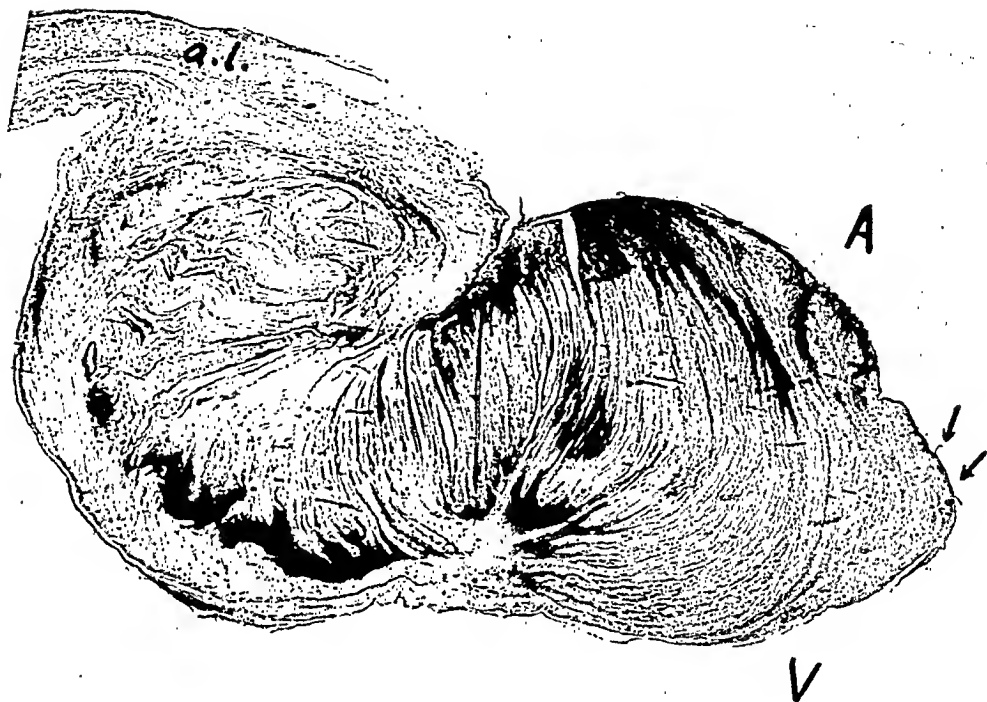


Fig. 6.—Case 4. Central, free-marginal sclerosis of aortic leaflet in "functional" aortic insufficiency. Section of a bicornate lesion ($\times 15$), showing dense, ovoid, nodular thickening attached to the end of a normal aortic leaflet (a.l.). In the latter, the original zonal structure is well maintained, and is free of vascularity or cellular infiltration. In only a small area at the extreme end of the nodule (marked by arrows), facing the aortic channel (A), is there a subendocardial cellular (histiocytic) infiltration. It is not visible in this low-power magnification. Ventricular surface (V); Weigert elastic stain.

Histologic Features.—Microscopic examination of the aortic leaflets showed that the valvular sclerosis was generally limited to the mid-portion of the free margins. Whatever lateral extension occurred progressed along the free margins; otherwise, the body of the leaflet remained normal down to its origin at the valvular ring. The division of the leaflet structure into generally well-defined zones—ventricularis, spongiosa, and fibrosa¹¹—was not distorted or obscured by inflammatory or degenerative changes (Figs. 6 and 7). The absence of vascularity and of focal cellular infiltration throughout the length of the leaflet suggested that the fibrous lesion at the site of the corpus arantii was not caused by chronic endocarditis of the rheumatic type. In the occasional case in which syphilitic aortitis was present, the preservation of the normal valve leaflet was a strongly contrasting feature.

Vertical section through the central part of the leaflet usually revealed the central lesion at the free margin as a round, sometimes ovoid-shaped, nodule of dense fibrotic tissue. In some cases the appearance of the nodule suggested that it was the result of repeated concentric lamination of thrombotic material, long since hyalinized. The acellularity was striking except at the extreme distal end and for a short distance on the aortic aspect of this extremity. Here there was a small number of histiocytes and fibroblasts beneath a slightly roughened, occasionally broken, endocardial surface. Scarcely any deposition of fibrin was noted in numerous serial sections. A very small area of progressive inflammation was apparent at the most distal part of the lesion, in contrast to the normal state along the length of the leaflet. This small area faced the aortic, rather than the ventricular, aspect, which differentiated it from verrucae of infectious origin, and suggested that pressure was exerted from above downward, rather than from the ventricular direction.

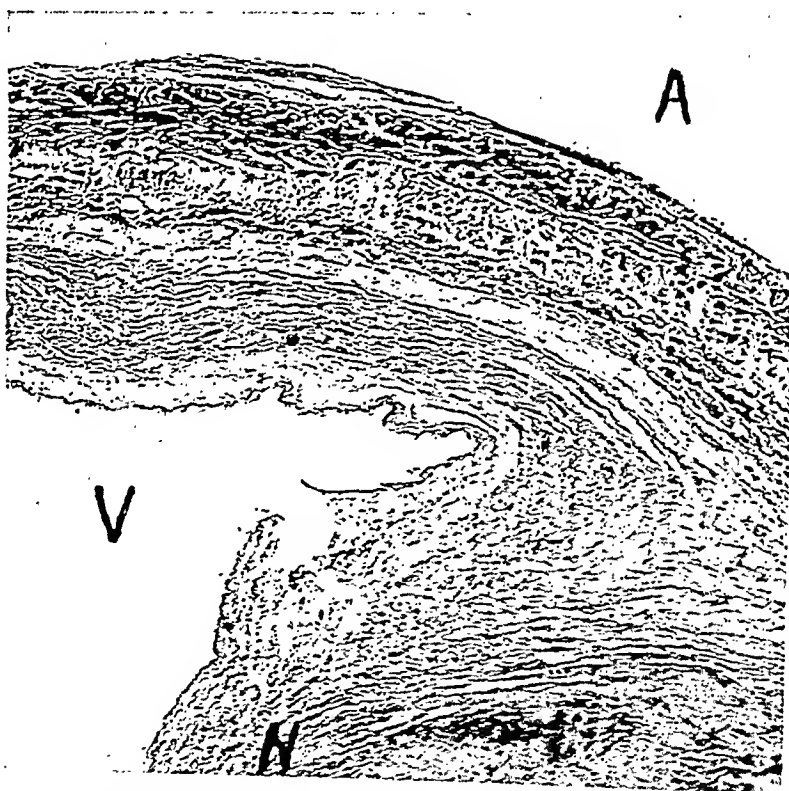


Fig. 7.—Case 4. Same as Fig. 6 ($\times 42$), showing free-marginal sclerotic nodule (N) at the end of a normal aortic leaflet. (A) Aortic aspect; (V) ventricular aspect. Weigert elastic stain.

Additional Clinical Data.—Ten of our eleven patients were men. There were six white patients and five Negroes. The youngest, and the only woman in the group, appeared much older than her stated age of 45 years. Nine of the remaining ten patients were 60 years of age or more; the oldest was 72 years.

Most, if not all, of these patients, including those with positive Wassermann reactions, had hypertension. Few eye-ground examinations were recorded, but the age of the patients, their usually elevated systolic blood pressure, and, finally, the pathologists' notes indicated that benign hypertension was the common cause of the "mechanical" aortic regurgitation.

The systolic blood pressure varied from 150 to 190, and the diastolic, from 35 to 100 mm. In nine of the eleven cases the diastolic pressure ranged from 50 to 75 mm.; a high diastolic pressure, i.e., 100 mm. or more, which has been reported as not infrequent by other observers,^{4, 5, 12} was noted in one of our patients.

These patients died of circulatory failure. Dyspnea, basal pulmonary congestion, and edema of the legs were features common to all. Pre-cordial pain was present in two cases. Although the majority did not survive their first attack of congestive failure, others gave a history of recurring attacks; one patient survived for six years. It is likely that these patients have the physical signs of aortic valvular disease for a much longer period than their short clinical course after the onset of failure would indicate.

Auricular fibrillation was present in five of the eleven cases. The following are brief clinicopathologic notes on five cases.

CASE 1.—H. H., a laborer, aged 66 years, was admitted to the Philadelphia General Hospital June 26, 1937, on the service of Dr. Henry Jump, with cardiac decompensation. He had been well until one month before, when he noticed increasing shortness of breath and edema of the legs. His past medical history was unimportant. He had seven children and denied any history of venereal disease.

Examination revealed a well-nourished colored man, with normal pupillary reactions. The bases of both lungs were filled with râles, the liver was enlarged, and edema of the legs was present. The blood pressure was 155/60. The heart was moderately enlarged, especially to the left, and auricular fibrillation was present. There was a double aortic murmur, consisting of a short systolic, and a predominant, blowing, diastolic murmur. The latter was transmitted down along the left border of the sternum.

The electrocardiogram revealed inversion of T_1 and T_2 and a slurred QRS, in addition to auricular fibrillation. The laboratory data included negative blood Kahn and Wassermann reactions and a blood urea nitrogen of 40 mg. per cent.

Death resulted from progressive cardiac failure on July 14, 1937. The clinical diagnosis was syphilitic aortic regurgitation and heart failure.

Necropsy (Dr. Merrill) revealed marked hypertrophy and dilatation of the left ventricle. The heart weighed 700 grams. The myocardium was firm, deep red, and 23 mm. thick in the upper lateral portion of the left ventricle. There was considerable dilatation of the aortic ring. The aortic valve circumference was 8.5 cm., the pulmonic, 8.0 cm., and the mitral, 11.5 cm. The aortic leaflets showed rolling and bicornate thickening at the central portion of the free margins. The bodies of the leaflets were practically normal, as were the commissures. No evidence of syphilitic aortitis was noted. There was slight thickening along the free margin of the mitral leaflet, apparently not rheumatic in origin.

Summary.—Hypertensive heart disease; hypertrophy and dilatation, especially of the left ventricle; and aortic insufficiency of the "mechanical" type.

CASE 2.—C. I., a white man, aged 70 years, was seen by one of us (E. S.) on Jan. 1, 1933, in the Paul Kimball Hospital, at Lakewood, N. J. The patient had a sudden attack of dyspnea which was a repetition of similar, but milder, attacks that had been occurring for several months. Examination revealed auricular fibrillation and a diastolic murmur at the third left intercostal space. The blood pressure was 175/80. The blood Wassermann reaction was negative. Fluoroscopic examination revealed enlargement of the left ventricle and a prominent aortic knob. The patient was discharged Jan. 9, 1933, with a diagnosis of hypertensive cardiovascular disease, but was readmitted Feb. 2, 1935, because of recurring dyspnea. The physical signs were as previously noted. The diastolic aortic murmur was pronounced, but limited to the third left intercostal space close to the sternum. The blood pressure was 160/45 and the pulse was of the Corrigan type. The patient left the hospital, improved, on March 19, 1935. It was decided later that syphilis was the probable cause of the aortic regurgitation, and, beginning in May, 1935, the patient received bismuth injections weekly for two months.

He was rehospitalized Nov. 19, 1935, because of circulatory failure; at this time the blood pressure was 138/45. The blood Wassermann and Kahn tests were again negative. Death occurred Dec. 12, 1935.

Necropsy revealed that the heart weighed 560 grams. The left ventricle was hypertrophied and dilated. The aortic valve was 7.8 cm. in circumference, the mitral, 10 cm., the tricuspid, 11.5 cm., and the pulmonic, 8.5 cm. Each aortic leaflet showed a central thickening of the free margin, consisting of irregular endocardial sclerosis. This was most pronounced in the posterior leaflet, where it extended along the free margin for 2.0 cm., and it spread down on the adjacent undersurface of the leaflet for 0.5 cm., forming a hard, protruding lip (Fig. 1). The central thickening of the right anterior leaflet was less prominent, but was marked by a small bicornate protuberance. In the left anterior leaflet the central lesion was a short, horizontal, rod-like thickening, 0.8 cm. long. The lateral portions of the free margins were normally delicate throughout. Commissure 3, the junction point of the adjacent portions of the posterior and left anterior leaflets, was widened, not by swelling or scarring, but apparently by a slight depression, suggesting that the lateral portions of the adjoining leaflets had been pulled away from each other. There was no calcific or sclerous thickening (arteriosclerosis) at the base of the aortic leaflets. Likewise, there was very little atheromatous or sclerotic degeneration in the aortic arch.

CASE 3.—C. M., a colored woman, who said she was 45 years of age, but appeared much older, was admitted on the service of Dr. D. Riesman, Sept. 10, 1935, complaining of shortness of breath and swelling of the legs and abdomen of three months' duration.

Examination revealed prominence of the neck veins and a blood pressure of 160/75. The heart was enlarged to the left; the apex was palpable beyond the midclavicular line in the fifth intercostal space. A loud, basal, diastolic murmur was heard behind the upper part of the sternum; its transmission was limited to the third left intercostal space.

Basal pulmonary congestion, hepatic enlargement, and edema of the legs were present and remained unaltered despite rest in bed and digitalization.

A Corrigan pulse was present, but no other peripheral signs of aortic regurgitation were noted.

The blood Wassermann reaction was negative. Death occurred Sept. 19, 1935. The clinical diagnosis was syphilitic heart disease with aortic regurgitation.

Necropsy (Dr. J. P. Welty) revealed that the heart weighed 400 grams and was transversely dilated. Section showed a soft, red myocardium, and a small, recent, myocardial infarct at the apex. Each aortic valve leaflet revealed thickening and lipping in the central portion of the free margin. The lipping was rounded in the right and left anterior leaflets, and gradually disappeared laterally into the normally delicate free margin. In the right leaflet this swelling was slightly eroded exactly in its center, giving rise to an early bicornate formation (Fig. 4). The posterior leaflet showed a larger and more irregular type of central thickening and lipping. There was no evidence of syphilitic aortitis.

CASE 4.—C. I., a white man, a merchant, aged 50 years, entered the Philadelphia General Hospital May 13, 1934 on the medical service of Dr. Thomas Klein, complaining of precordial pain and dyspnea, each of one month's duration. The patient noted palpitation and some edema of the ankles shortly before admission. Examination revealed pulmonary basal congestion and congestive enlargement of the liver. The blood pressure was 180/35. The heart was enlarged to the left. There was a double aortic murmur, but the diastolic murmur was predominant. Numerous extrasystoles were present. Urinalysis showed a cloud of albumin and numerous hyaline casts. Death was preceded by progressive azotemia. The blood Wassermann reaction was strongly positive.

Necropsy (Dr. Ingleby) revealed that the heart weighed 550 grams. Both ventricles were dilated, and the left was also moderately hypertrophied. Section revealed a rather soft myocardium without gross lesions. The coronary vessels were normal throughout. The aortic valve leaflets showed a striking deformity, namely, sclerotic thickening along the mid-portion of each free margin which had replaced the corpora arantii. It was a horizontal, cylindrical thickening, about 1.5 cm. long, with lateral bicornate projections (Figs. 2 and 3). The lateral portions of each leaflet were normally delicate, and the commissures were also normal, despite the adjacent development of syphilitic aortitis. The central, free marginal lesions were very firm. Their size, consistency, and shape were not those of ordinary verrucae. The aortic valve circumference was 8.6 cm., the mitral, 11.0 cm., the pulmonary, 8.2 cm., and the tricuspid, 13.0 cm. The mitral valve was normal, as were the other valves.

Summary.—Left ventricular hypertrophy and dilatation; aortic regurgitation without commissural involvement; dilatation of the aortic ring; syphilitic aortitis; central free marginal sclerosis (bicornate lesions of "mechanical" regurgitation).

CASE 5.—J. M., a colored man, aged 66 years, was admitted to the Philadelphia General Hospital March 9, 1936 on the service of Dr. E. Eliason for hemorrhoidectomy. He was aware that he had high blood pressure and "heart trouble," but could give no approximate date of onset. He had sharp precordial pain, especially at night, accompanied by dyspnea. Edema of the ankles in the evening had been present for ten months. He was a laborer, and had seven children, all in good health.

His blood pressure was 208/80 and 225/80 in the left and right arms, respectively. There was marked cardiac enlargement both to the left and right. A systolic thrill was palpable at the base of the heart, and a rough systolic murmur in this area was transmitted to the vessels of the neck. It was followed by a loud, slapping diastolic murmur which was transmitted to the third and fourth left intercostal spaces. At this time the cardiac rhythm was normal. A Corrigan pulse was noted.

There was no evidence of congestive heart failure. The blood Wassermann and Kahn reactions were negative. Fluoroscopic study showed marked enlargement of the left ventricle and a greatly widened aortic arch.

The patient was readmitted to the medical service of Dr. S. Loewenberg, June 20, 1940, with paroxysmal dyspnea and cardiac decompensation. He had auricular fibrillation and signs of aortic valvular disease, as outlined above. The serologic reactions were again negative. He was readmitted Oct. 30, 1940, with recurring decompensation. His blood pressure then was 180/70. Attacks of substernal pain were relieved by nitroglycerin. Systolic and diastolic thrills were again palpable over the base of the heart, and a double aortic murmur was heard; the diastolic murmur was strikingly harsh and prolonged. The Wassermann reaction remained negative.

On his sixth and final hospitalization (service of Dr. Wm. Leaman, May 3, 1941) the blood pressure was 180/60. The physical signs were unchanged. On each previous admission the diagnosis had been syphilitic heart disease with aortic regurgitation. The diagnosis now became doubtful because the serologic tests for syphilis had been consistently negative, and because the survival period was rather prolonged. Digitalization was of no avail, and the patient died of congestive failure on June 9, 1941.

Necropsy (Dr. Conforth) revealed marked hypertrophy of the left ventricle. The heart weighed 700 grams. The myocardium was firm, 28 mm. thick in the upper part of the left ventricle, and revealed no focal scarring or necrosis. The coronary arteries were patent throughout, showing little sclerosis. The aortic valve leaflets were enlarged because of marked dilatation of the root of the aorta. The central portions of the free margins of the leaflets were thickened and lipped. The right aortic leaflet, in addition, was everted almost its entire length. Commissures 1 and 2 were normal; in 3 the component leaflets (posterior and left anterior) were about 2 mm. apart, evidently having been pulled away from each other. There was no evidence of syphilitic aortitis. The circumference of the aortic ring was 8.0 cm., but, as a result of a remarkable, sacular, onion-shaped dilatation of the root of the aorta, the aortic circumference on the line of the commissural attachment was 12 cm. There was a difference of at least 4 cm. in the circumference of the aorta at this level and at the aortic ring.

DISCUSSION

We were unable to include this type of aortic regurgitation in the current classification of valvular disease. We wish to emphasize that these aortic valvular lesions may develop in any heart in which the aortic valvular ring has dilated; therefore, they are devoid of etiologic significance. We have noted them even in young and middle-aged patients with rheumatic heart disease, but always in the presence of a dilated aortic ring. This report is concerned primarily with the usually elderly hypertensive persons whose aortic regurgitation remains etiologically a matter of doubt, and who constitute a group which is entirely different from that of typical aortic insufficiency of infectious origin. The possible importance of arteriosclerotic degeneration as an etiologic factor in such cases must be considered. Osler, who described "arteriosclerotic" regurgitation,² thought that the lesion was similar to that of chronic endocarditis. Today we know that the aortic valvular lesion caused by arteriosclerotic degeneration is characterized by (1) calcareous infiltration beginning at the bases, and later involving the bodies, of the leaflets, the corpora arantii, and the sinuses, and (2) by the yellow, opaque, subintimal infiltration of atheroma. The lesions of

"mechanical" regurgitation are clearly different. We also know that arteriosclerosis of the aortic valve leaflets causes stenosis rather than regurgitation. It is likely, however, that some of Osler's cases were identical with those herein described, for he mentioned, under the heading "relative insufficiency," the infrequent occurrence of aortic regurgitation associated with dilatation of the aortic ring and adjacent arch.

The valvular lesions in most of our cases were prominent enough to engage the attention of the pathologist. In some cases not included in this series, the lesions were slightly developed, and consequently dismissed as being insignificant. Clinical observations, however, revealed the presence of aortic valvular insufficiency. On the other hand, we have not infrequently noted this type of valvular sclerosis in the absence of any clinical record of aortic regurgitation. The pulse pressure in such cases was invariably increased, and one may suspect that short diastolic aortic murmurs, with little or no transmission, may have been missed by the examiner.

Since dilatation of the aortic ring or supravulvular dilatation appeared to be the cause of this type of aortic insufficiency, it is likely that the valvular lesions were the result, rather than the cause, of the insufficiency. The normal aortic leaflets were unable to meet the demand for increased coverage, and, despite compensatory elongation (often seen), they were unable to prevent a leak. The regurgitation in the beginning was probably very slight, gradually eroding the corpora arantii and eventually giving rise to the lesions herein noted. These lesions may thus be regarded as an example of structural change secondary to functional insufficiency. The recognition of these lesions is not unimportant, in our estimation, for they appear to be characteristic. They lend credence to the opinion once held by some clinicians that functional aortic valvular insufficiency is an entity, and that it can exist despite the presence of diastolic hypertension.⁴ The absence of objective evidence made the question hypothetical. Dilatation of the aortic ring was not regarded as satisfactory evidence, for terminal relaxation of heart chambers and their valvular rings is a common occurrence. The time factor is of some importance, which may be the explanation of reports of aortic insufficiency which was termed "functional" because there was no pathologic valvular change. It is our impression that few patients with aortic insufficiency show a complete absence of valvular deformity. The differential diagnosis in elderly persons is concerned chiefly with the possibility of syphilitic infection. We have previously pointed out that positive serologic reactions may be anticipated in at least 95 per cent of all patients with truly syphilitic aortic regurgitation, excluding those who have recently had specific treatment.¹³ This is in contradiction to the 65 per cent or 70 per cent of positive reactions in uncomplicated aortitis. This conclusion was reached after study of necropsy material in which we segregated the occasional cases of "mechanical"

regurgitation and of healed dissecting aneurysm with aortic regurgitation which not infrequently are regarded as syphilitic because of the deceptive gross appearance.¹³ The serologic reactions are thus of great importance in the analysis of these cases. We now believe that aortic regurgitation in untreated patients more than 50 years of age should not be considered syphilitic if the blood Wassermann and Kahn reactions are repeatedly negative. This single criterion appears to be reliable regardless of the patient's race or occupation, or any other factor that may ordinarily influence the diagnosis. The presence of auricular fibrillation in a case of aortic regurgitation in which the serologic reactions are negative almost certainly indicates that the lesion is not syphilitic. When "mechanical" regurgitation is accompanied by positive serologic reactions (a minority in our group), the diagnosis will remain, in most instances, an enigma until the day of necropsy. However, the presence of a loud, snapping aortic second sound, in addition to the diastolic aortic murmur, is suggestive of dilatation of the aortic ring, as pointed out by Scott.¹⁴

SUMMARY

Some persons, mostly men beyond middle age, exhibit signs of aortic regurgitation which is not caused by syphilis, rheumatic heart disease, bacterial endocarditis, or arteriosclerotic degeneration. Hypertensive cardiovascular disease is usually present.

This type of aortic regurgitation may be unaccompanied by most of the peripheral phenomena which are characteristic of aortic insufficiency of infectious origin. The diastolic murmur is usually merged with an accentuated aortic second sound. Patients with this lesion eventually die of congestive heart failure. Preordial pain is infrequent. Auricular fibrillation is common.

Dilatation of the aortic ring is present in most cases. Occasionally, only supra-avalvular dilatation of the aortic arch occurs. In all cases the aortic leaflets appear insufficient to meet the need of increased coverage. They often show compensatory elongation. Depending on the length of the survival period, there is a variable development of structural changes in the aortic leaflets; this is apparently secondary to the dilatation of the aortic ring and is brought about by the eroding action of slow leakage. The change consists of a sclerotic thickening of the mid-portion of the free margin of the leaflet, without involvement of the commissures. The latter, however, may be slowly pulled apart in the course of marked ring dilatation. Bicornate lesions and sclerotic lipping in the mid-portion of the free margins of the leaflets are characteristic of this type of regurgitation.

Syphilis may coexist in some cases; it may cause aortitis without involving the aortic valvular structure. Occasionally there may be both ring dilatation ("mechanical" insufficiency) and true syphilitic aortic valvular disease.

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THE ROUTINE USE OF CEDILANID IN CLINICAL PRACTICE

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EVER since Withering first broke down the herb medicine of the village witch and discovered that it was the foxglove which acted upon "the dropsy," research workers all over the world have been attempting to break up digitalis into its active ingredients. One glycoside after another, each supposedly free of toxic effects, has been isolated and recommended as the active principle of digitalis. These claims, however, have never been substantiated clinically, and the perfect cardiac drug has remained the will o' the wisp of the cardiologist. Therefore, when Stoll¹ isolated a glycoside from *Digitalis lanata* which differed from any of those in the *Digitalis purpurea* group, a new incentive was given to this search for the drug of choice in heart failure. This new glycoside has been called Lanatoside C, or Cedilanid.

To begin with, it is important to realize that the use of digitalis in the form of the whole leaf has marked disadvantages. The most important of these, from the clinician's point of view, is that there has never been a completely satisfactory method of assaying the preparation so that any tablet of digitalis leaf will always produce the same result in any given case. Gold and his co-workers² proved this point by some excellent research which most clinicians had known about for many years. Their carefully controlled experiments showed that, although the cat method of bio-assay was more nearly parallel to the efficacy of the drug in man, the frog method, on the other hand, bore almost no relation to the action of the drug on the human heart. Moreover, the cat method cannot be entirely relied upon, because patients take digitalis by mouth, and its glycosides are absorbed differently from various gastrointestinal tracts, whereas, in the cat method of assay, the drug is given intravenously, and absorption plays no role.

For a long time we, like many others, have felt the need for a preparation the action of which in any given case would be known at all times, so that no matter where the patient bought his digitalis, we could expect a specific action from a given amount of the substance. In our cases we had used practically all of the previously isolated glycosides without much success. In reviewing the literature, we came upon the work done on Cedilanid and immediately became interested in its use.

Experimentally it has been shown that this glycoside has a greater margin of safety than all the other *Digitalis lanata* glycosides, and, at the same time, brings about greater cardiac efficiency.³ It has also

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been shown in animals that Lanatoside C will not produce a significant reduction in coronary blood flow, as measured by the thermostromuhr.⁴ After this experimental work on animals, Fahr and LaDue⁵ began to use the drug on a large group of patients in the Minneapolis General Hospital. When auricular fibrillation was present, its action was quite rapid and effective. They observed that in the treatment of congestive heart failure its action was excellent, even in the presence of normal sinus rhythm. They also met with good results in auricular paroxysmal tachycardia and auricular flutter, and they came to the conclusion that this preparation is less toxic in many instances than *Digitalis purpurea*. They found that the substance is stable, and, in therapeutic doses, does not damage the heart muscle of the dog even when administered daily for a period of three months.

Sokolow and Chamberlain⁶ gave Cedilanid intravenously and found that its rapidity of action was its most striking clinical feature. They continued their studies, using both the oral and intravenous preparations, and concluded that the rapid absorption, constant potency, and rapid action of Cedilanid gave it definite advantages over *Digitalis purpurea*.⁷

We selected a mixed group of hospital outpatients, hospital-ward patients, and private ambulatory and bedridden patients. Seventy-five per cent of these had been receiving digitalis for varying periods of time, and we were well aware of the difficulties involved in controlling their maintenance dosage; the remaining 25 per cent had never taken digitalis. The average total oral dose for digitalization was 15 to 20 tablets of Cedilanid (7.5 to 10 mg.). When the rapid and massive method of digitalization was used, the total dose of Cedilanid was approximately 10 to 15 tablets (5 to 7.5 mg.). The average maintenance dose was 1 to 3 tablets daily (0.5 to 1.5 mg.). Ninety-eight per cent of the group responded to the oral administration of Cedilanid admirably. The usual criteria for improvement were used, namely, disappearance of edema in the lower extremities, of ascites, and of enlargement of the liver, reduction in pulse rate, lowering of venous pressure, and electrocardiographic evidence. Almost uniformly the action began sooner than that of digitalis leaf preparations, and the drug was also eliminated more rapidly. Most important of all was the fact that, once a maintenance dose was established, this could be continued indefinitely, providing the patient had no sudden change in his condition brought about by overexertion or coronary failure.

Two of the one hundred patients thus studied, of whom one had received digitalis and the other had not, both of whom had chronic auricular fibrillation, could not be controlled by the oral administration of Cedilanid, even when the dose was increased to 0.5 mg. six times a day. Both patients responded well to whole leaf digitalis. We have no way of explaining this peculiar fact, except that in certain

cases more than one glycoside may be necessary, or that some glycoside other than Lanatoside C may be the only one capable of acting under certain conditions. Only carefully controlled animal experiments can settle this question.

Judging from our experience with Cedilanid, it has a definite place in the armamentarium of the cardiologist. It is true that in large enough doses it will give the same toxic effects as *Digitalis purpurea*; nevertheless, the margin of safety is greater, and the rapid elimination of the drug diminishes the duration of the toxic symptoms. Finally, let us reiterate that once the dosage has been established, one need not worry about the possibility that each new prescription may be stronger or weaker, for we are dealing with a crystalline substance which is standardized by weight, and is therefore not subject to the variations of bio-assay.

SUMMARY

1. The pharmacology and chemistry of Cedilanid (Lanatoside C) are reviewed briefly.
2. The oral preparation was found to be constant in its action in clinical practice.
3. It was effective in ninety-eight of one hundred cases in which it was tried. No apparent cause for its failure could be found.
4. In those cases in which Cedilanid was effective, its toxic action was similar to that of *Digitalis purpurea*, but passed off more quickly.
5. Cedilanid is an efficient glycoside of *Digitalis lanata*, and has a definite place in cardiac therapy.

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THE ELECTRICAL CONDUCTIVITY OF THE TISSUES NEAR THE
HEART AND ITS BEARING ON THE DISTRIBUTION OF
THE CARDIAC ACTION CURRENTS

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IN THEORETICAL studies of the factors which determine the form of the electrocardiogram, it has usually been assumed that the heart is, in effect, immersed in an extensive medium which may be regarded as homogeneous with respect to those properties which determine the distribution of electrical currents of the kind produced by the heartbeat.¹⁻³ Those who have made this assumption have not maintained that it is strictly in accord with the facts, but merely that, considering the purposes which they had in mind, it represents the true situation with adequate accuracy. Recently the validity of this claim has been challenged as a result of the interpretation placed upon indirect experiments of various kinds.⁴⁻⁷ So far as the writers have been able to ascertain, however, systematic direct measurements of the specific electrical resistances of the living tissues of anesthetized mammals have not previously been made. This is because of the great technical difficulties encountered in the application to such tissues of the methods available to the physical chemist for the measurement of specific conductivity, properties, and use of simple electrode systems which we have employed to measure the specific resistances of living tissues *in situ*.

Theoretical Considerations.—The current flow through an electrolyte or other conductor in an ordinary conductivity cell is determined by the size and shape of (a) the electrodes and (b) the walls of the cell. In the simplest case of plane circular electrodes, located at the ends of a cylindrical tube and perpendicular to its axis, the resistance, R , is defined by the equation

$$R = TL/A$$

where T is the specific resistance; L , the length of the tube; and A , its cross-sectional area. The cell constant is then $K = R/T = L/A$. For more complicated cell forms the cell constant is usually determined experimentally by the use of an electrolyte of known specific resistance, T . For the present purpose, however, it is not practical to obtain nonelectroconducting boundaries corresponding to the walls of a cell from which the cell constant may be computed or measured. The obvious expedient is then to consider an unbounded or infinite medium.

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The resistance between two small spherical electrodes of radii a and b separated by a distance l in an infinite medium of specific resistance T is given by Mason and Weaver¹⁷ as

$$R = T/4\pi \left(\frac{1}{a} + \frac{1}{b} + \frac{2}{l} \right) \quad (1)$$

As l is made large its effect becomes negligible, and the resistance is the sum of two parts, one for each electrode. The cell constant for a single spherical electrode is then $\mu = 1/4\pi a$. Similarly, for a buried disc of radius a , $\mu = 1/8\pi a$, and if the disc rests on a flat surface of the medium, $\mu = 1/4\pi a$.

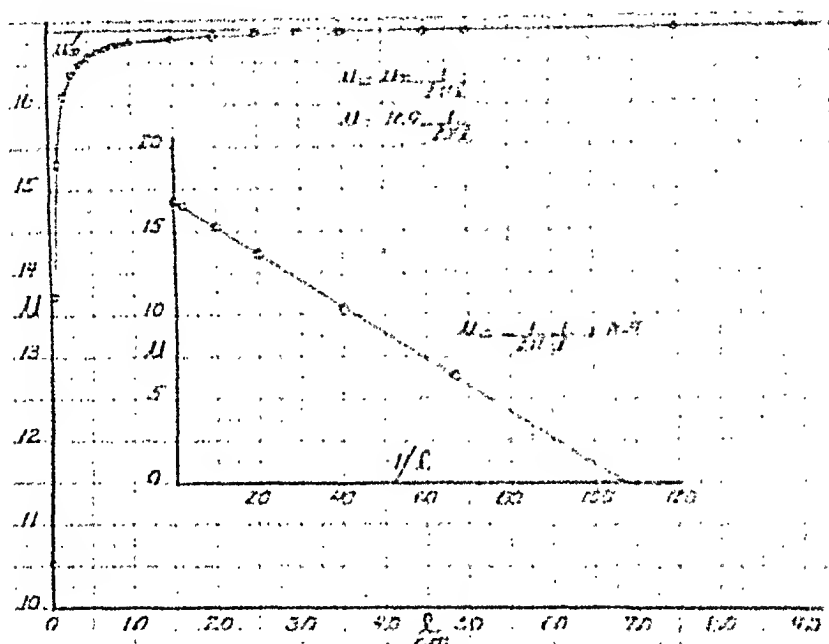


Fig. 1.—Curves showing the relation between the cell constant, $\mu = R/T$, of a pair of point electrodes placed in an infinite medium and the distance between them, l . The large graph represents the equation $\mu = 1/4\pi \left(\frac{1}{a} + \frac{1}{b} + \frac{2}{l} \right)$, which was obtained by substitution of values for a and b and a and b in Equation 2 (see text). The small insert shows that when μ is plotted against $1/l$, a straight line is obtained.

The most practical experimental technique has been to use cylindrical wires which were insulated except at the ends. The electrodes in contact with the electrolyte or tissue were then circular discs with the diameters of the wires. With thick insulation the cell constant of each electrode would be that of a disc applied to the surface, or $\mu = 1/4\pi a$. The cell constant has not been calculated for thin insulation, but it will be smaller than $1/4\pi a$, and will probably approach the value $1/8\pi a$, which is that of the buried disc with both faces exposed. In general then, we may write

$$R = T \left(1/\alpha a + 1/\beta b + 1/2\pi l \right) \quad (2)$$

where α and β depend upon the shapes of the electrodes and the insulation, but certainly lie between 1 and 4π . The relation between $\mu = R/T$ and l is shown in Fig. 1. If a and b are nearly equal and l is more than

twenty times the radius a , the proximity effect will be less than 5 per cent. The requirement of an infinite extent of a single tissue cannot be met rigorously, and the effects of adjacent tissue have been calculated. It has been found that if each electrode is more than twenty times its radius from the nearest surface, the boundary proximity effect is less than 5 per cent for any conductivity of adjacent tissue from zero to infinity.

If two electrodes are placed more than twenty times their radii from each other and from the boundaries, the cell constant should be within 10 per cent of the value for a large separation in an infinite medium. For any particular organ or tissue these conditions can always be met by making the electrodes sufficiently small, but other difficulties may arise. The electrodes should not be as small as the tissue cells, for the measured resistance will then depend upon their position relative to the nearest cells. Furthermore, as the electrodes are made smaller, the polarization impedance of the electrode surface increases more rapidly than the measured resistance. A limit is then set by the efficacy of the platinization which can be obtained. In the case of a disc, the platinization near the center is not fully effective because the current density is much lower there than it is near the edge.

Equipment.—A portion of the work reported here was performed in the Electrochemical Laboratory and the remainder in the Heart Station. As regards essentials, the equipment was the same in both places. It consisted of a modified Jones and Josephs⁸ bridge, which measured parallel resistance (R_p) and capacity (C_p), a thermostat, a standard conductivity cell of a design recommended by Jones and Bollinger,¹⁰ an oscillator, and platinum electrodes of various types. The bridge used in the Heart Station differed from that employed in the Electrochemical Laboratory in that it had an amplifier in the phone circuit. The oscillator used in the latter place had a fixed frequency of 1,000 cycles per second and a fixed output, whereas both the frequency and the output of the oscillator used in the former could be varied. The small electrodes hereinafter designated as point electrodes, or points, were made of platinum wire about 0.25 mm. in diameter and were insulated except at the tips by a variable thickness of glass.

EXPERIMENTAL RESULTS

Measurements of Point-Electrodes Systems.—Measurements were made with point electrodes in different combinations, at various separations, and in several media and shapes and sizes of vessels. Only those pertinent to the present investigation will be discussed. Aqueous solutions of sodium chloride, potassium chloride, ammonium chloride, hydrogen chloride, and zinc sulfate were used. For certain experiments the electrolyte was dissolved in 2 per cent agar-agar (Difco Bacto-Agar), which was subsequently allowed to solidify. The resistance of all aqueous solutions was measured in the standard conductivity cell be-

fore and after it was measured with the special electrode systems. A 3-liter beaker filled with the solution to be studied served as a first approximation to an infinite medium.

Electrode Polarization and Platinization.—The polarization impedance at the surface of bare platinum was too large to permit the use of small electrodes of this material; consequently, all electrodes were electrolytically coated with platinum black before they were used. The point electrodes were platinized by passing current from a storage battery through them after they had been immersed in chloroplatinic acid. A commutator was used to reverse the polarity of the current once per second. The resistance in the external circuit, which was located mainly at the electrode-acid junction, varied continuously in an unknown fashion as the degree of platinization increased. As the elec-

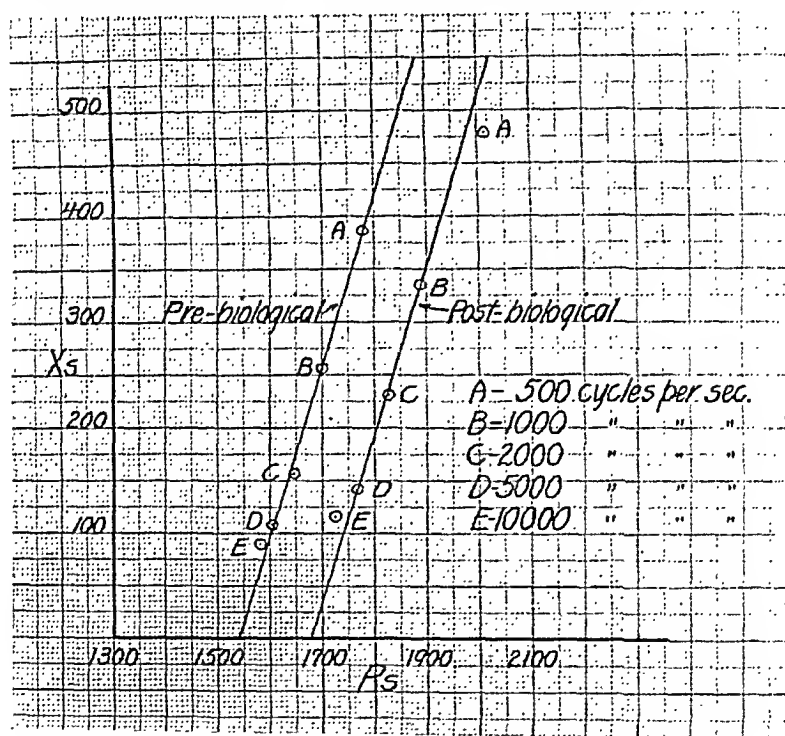


Fig. 2.—Impedance loci of a pair of point electrodes before and after they were used to measure the resistance and reactance of living tissue.

trodes were platinized for increasing lengths of time, the effects of polarization at first decreased rapidly and then more slowly (Jones and Bollinger¹²). After 150 seconds of platinization, the electrodes were usually satisfactory. The series resistance and reactance of such a pair of electrodes in normal saline were computed from the measured parallel resistance and capacity, and are plotted as an impedance locus in Fig. 2. The intercept on the resistance axis is the electrolyte resistance approached at high frequencies. The reactance and added

resistance at each frequency constitute the electrode polarization impedance. For many purposes this is negligible. It was found, however, that for measurements made at the single frequency of 1,000 cycles, the apparent cell constant of point electrodes increased as either the concentration or the temperature of the electrolyte was increased. For unselected electrodes the changes in the value of μ produced by variations in the temperature and concentration of the solutions studied amounted to between ± 4.5 and ± 8.5 per cent of its mean value. For any given concentration, μ was constant for a given pair of electrodes (separated by a distance of at least 3 cm.) to within 0.5 per cent. This constant did not vary with changes in the output of the oscillator at any frequency. These effects are probably results of the changes of the polarization impedance with concentration and temperature.

When two point electrodes were immersed in a 3-liter "infinite" medium, the point-point resistance and μ increased gradually with greater separation of the electrodes, but this increase was most rapid when the separation was less than 1 cm. From the data of Table I it was found that $\mu_{\infty} = \frac{1}{\alpha a} + \frac{1}{\beta b} = 16.9 \text{ cm.}^{-1}$. If $a = b = 0.125 \text{ mm.}$ then $\alpha = \beta = +9.5$. This lies between the values of 8 for the double-sided disc, and 4π for the sphere, indicating that the surface was probably convex outward. Substituting this value in equation (2), the theoretical curve of Fig. 1 was obtained. It agrees well with the observations, and shows a proximity effect of 5 per cent for a distance of 2 mm.

TABLE I

COMPARISON OF THE OBSERVED VALUES OF μ AND THOSE CALCULATED FROM THE EQUATION, $\mu = \mu_{\infty} - \frac{1}{2\pi l}$, OF FIG. 1

lcm.	CALCULATED	μ	OBSERVED
0.5	16.58		16.65
1.0	16.74		16.74
			16.81
4.0	16.86		16.81
4.5	16.86		16.86
5.0	16.87		16.88
10.0	16.90		

When the volume of the medium was reduced from 3,000 to 60 c.c. and the diameter of its cross section from about 15 cm. to 4.5 cm., the resistance and the relation between the resistance and the distance between the electrodes were the same (within the physical limitations as regards separation of the electrodes imposed by the smaller volume of the medium) as when the medium was more extensive. The data given in Table II indicate that the electrode proximity effect and the boundary proximity effect are about 1 per cent for the range investigated.

TABLE II

VALUES OF THE CELL CONSTANT, μ , OF A PAIR OF POINT ELECTRODES IN A RESTRICTED MEDIUM (60 C.C. OF NH_4Cl SOLUTION IN A CYLINDER 4.5 CM. LONG, AND 4.5 CM. IN DIAMETER) AND IN A MORE EXTENSIVE MEDIUM (3,000 C.C. OF NH_4Cl SOLUTION IN A LARGE BEAKER)

	DISTANCE BETWEEN ELECTRODES, μm .	μ
Restricted medium	1.5	18.69
Restricted medium	2.0	18.77
Restricted medium	2.5	18.84
Unrestricted medium	1.5	18.90

When 2 per cent by weight of agar-agar was dissolved in aqueous solutions of a number of inorganic substances and permitted to solidify, it caused no change in the conductivity of the original aqueous solutions. The resistance-distance relationship of the point-point electrode system inserted into the agar block was the same as for a medium of the original composition and of comparable shape and volume.

As a test of our method, we calculated from point electrode measurements the resistance that would be observed when the medium was placed in a standard conductivity cell, and then attempted to confirm our prediction by observation. Since $R_k/R_\mu = K/\mu$, the factor K/μ may be ascertained by measuring the resistance at a given frequency of a solution of known conductivity by both methods. When R_μ has been measured with an unknown solution, R_k may be calculated. As a check, R_k for the unknown solution may be measured directly. For example, the resistance (R_k) of an aqueous solution of approximately 0.9 per cent NaCl measured 2,574 ohms in the standard conductivity cell. The predicted value of R_k for an agar block containing 2 per cent agar-agar dissolved in 0.9 per cent NaCl, obtained by computation from R_μ , was 2,584 ohms.

Summary on Electrode Systems.—The properties of simple point-electrode systems were investigated theoretically and experimentally with reference to their suitability for the measurement of specific conductivities under a variety of conditions. In the form used by us these special electrode systems have certain limitations and do not permit measurement of specific conductivity with the same degree of precision as the standard conductivity cell. They do, however, make it possible to ascertain, with an accuracy sufficient for many purposes, the specific conductivity of materials which cannot be placed in a standard conductivity cell and have not heretofore been satisfactorily measured.

MEASUREMENT OF THE SPECIFIC RESISTIVITY OF LIVING MAMMALIAN TISSUES

Our animal experiments were carried out upon dogs which were anesthetized with morphine and urethane. Various operative procedures were used to gain access to the organs or tissues studied. When the chest was opened, the lungs were ventilated with room air by

TABLE III
MEASUREMENTS OF THE SPECIFIC RESISTANCE OF LIVING TISSUE IN OHM CM.

DATE	MUSCLE	LIVER	LUNG	HEART	PERICARDIUM	FAT	BLOOD	SERUM
1938								
4/28	492-506 425-416	524-460 513	768-791 810-757 784-839 713 *401 624	153-143 307-285	434-405			
5/9	707-565	1,083-789	850-719	212-199				
5/12	722-525 752 701-569	517-419	†1,368-1,332					
5/17	552-539 587-527	778-758	†1,503-1,243	265-251 224-212		1,960-1,757		
5/19	636-672		765-681					
5/20	1,103-938					2,450-1,859		
6/1	426		897-804 686-615					
6/4	1,532-760	697-390	†1,278-1,108	185-151				
6/6	610-320	595-222	†1,257					
6/7								178-98
6/9							235-195 225-175	

The figures given first are those based on the prebiologic calibration of the point electrodes.
The figures given last are those based on the postbiologic calibration of the point electrodes.

*Lungs deflated.

†Lungs superinflated.

means of a pump designed by Erlanger and Gesell.¹⁴ All measurements of tissue conductivity were preceded by the calibration of a set of two point electrodes separated by a distance of 2 or more centimeters. The calibration consisted of measuring, at frequencies of 500, 1,000, 2,000, 5,000, and 10,000 cycles per second, the parallel resistance and parallel capacities required to balance the bridge after the electrodes were immersed in an "infinite" medium of approximately 0.9 per cent saline at a temperature close to that of the tissues to be studied. The conductivity of the 0.9 per cent saline, maintained at the same temperature, was measured independently in a standard conductivity cell. As soon as the point electrodes had been standardized, they were placed on the surface or within the substance of the tissue or organ under investigation, and the parallel resistance, R_p , and parallel capacitance, C_p , required to balance the bridge for the above frequencies were ascertained as rapidly as possible. After the tissue measurements were completed, the electrodes were restandardized.

TABLE IV

AVERAGE VALUES FOR THE SPECIFIC RESISTANCES OF LIVING TISSUES IN OHM CM.

TISSUE	NO. OF ANIMALS	NO. OF OBSERVATIONS	SPECIFIC RESISTANCE PREHOL. CALIBRATION	SPECIFIC RESISTANCE POSTHOL. CALIBRATION
Muscle	9	13	711	
(somatic)	9	11		575
Liver	6	7	672	
	6	6		506
Heart	4	6	224	207
Pericardium	1	1	434	405
Lung				
At end of normal inspiration	4	9	766	
		7		744
Superinflated	4	4	1,367	
	3	3		1,227
Deflated	1	1	401	
Fat	2	2	2,205	1,808
Serum		1	178	98
Blood		2	230	185

The specific resistance of the saline solution (approximately 0.9 per cent) used in standardizing the point electrodes was roughly 50 ohm cm. at 37° F., or about one-fourth that of defibrinated blood.

The series resistance and reactance at each frequency were calculated for the electrodes in saline before and after the tissue measurement.* The characteristics in each case are shown in the impedance loci of Fig. 2. The "cell" constant and the electrode polarization were not the same after the electrodes had been in contact with tissue as

*In computing the series resistance, R_s , and series reactance, X_s , the following formulas were employed (see Cole and Cole¹⁵):

$$R_s = \frac{R_p}{(1 + R_p^2 C_p^2 W^2)} \quad X_s = \frac{R_p^2 C_p W}{(1 + R_p^2 C_p^2 W^2)}$$

R_s = Series resistance; X_s = series reactance; R_p = parallel resistance; C_p = parallel capacitance; $W = 2 \pi$ frequency.

before, perhaps because of the absorption of proteins. The specific resistance of the tissue and the polarization corrections were calculated from these data. Higher values for the specific resistivity of the tissue were usually obtained when the first or prebiologic calibration curve was used than when the second or postbiologic calibration curve was used, but the reverse was sometimes the case (Tables III and IV). It should be pointed out in this connection that since several tissues were measured with the same pair of electrodes in the course of each experiment, the prebiologic calibration for all except the first tissue studied was also the postbiologic calibration for the preceding observation. In some instances the series resistance and reactance of the tissue were calculated, and the polarization resistance and reactance subtracted at each frequency.

The impedance loci for muscle, liver, and lung shown in Figs. 3, 4, and 5 were obtained by plotting the resistances and reactances which had been computed in this manner. These loci are probably circular arcs such as have been found over wider frequency ranges for other tissues and cells.^{15d, 15f} It is possible to extrapolate the lower frequencies and direct current resistances from these data. However, the resistance for the range of frequencies below 500 cycles per second, which occur in the electrocardiogram, are only slightly larger than those at 1,000 cycles. Consequently, only these latter values will be considered.*

The simplest biologic tissue studied was defibrinated dog's blood, which consisted, by volume, of half cells and half extracellular fluid. About 500 c.c. of defibrinated blood in a beaker with a diameter of 10 cm. constituted the "infinite" medium. The electrical resistance was measured both in the standard conductivity cell and by calibrated point-electrode systems. The resistance and capacitance measured by the point electrodes in a large medium are resident in a relatively small volume of circumelectrode medium, and are not influenced to any great extent by the medium lying outside this region. This is shown by measurements made by immersing the point electrodes in defibrinated blood before and after the blood was allowed to sediment. The resistance of the mixed whole blood was 4,900 ohms; whereas, after sedi-

*The specific resistances shown in Table III were computed in the following way. Approximately 0.9 per cent saline solution at body temperature was measured in a standard conductivity cell at the beginning and again at the end of the experiment, and the mean of the two readings (R_K) was used. The cell constant of the conductivity cell, K , was known to be 39.37. The same solution was measured with the point electrodes before and after each observation. The prebiologic constant of the point electrodes was ascertained from the first reading, $R\mu$ (at 1,000 cycles per second), by the formula:

$$\mu = K \frac{R\mu}{R_K}$$

The postbiologic value for the cell constant (μ) of the point electrodes was ascertained from the second reading in the same way. The specific resistance of the tissue was computed by dividing the measured resistance of the tissue at 1,000 cycles per second by the cell constant.

mentation was complete and the electrodes were in the serum, a reading of 2,940 ohms was obtained. The latter value was evidently due largely to the resistance of the serum.

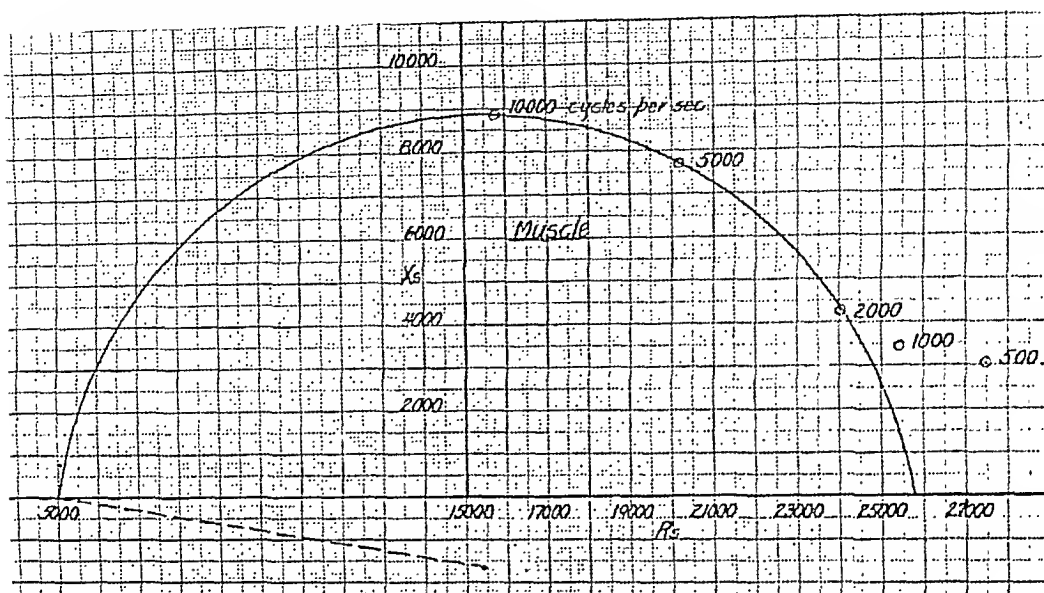


Fig. 3.—Impedance locus of triceps muscle based on experiment of May 19, 1938.

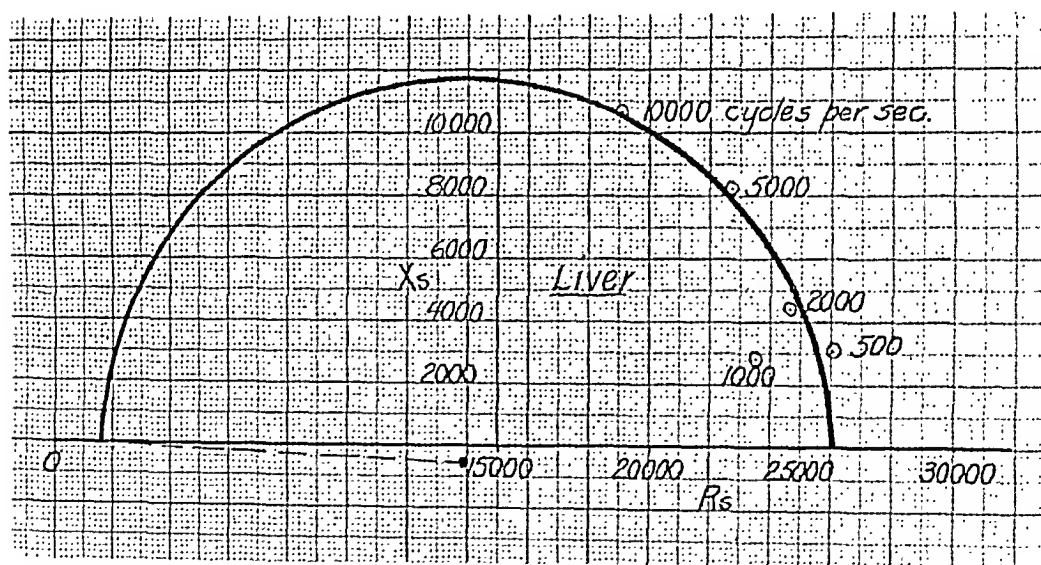


Fig. 4.—Impedance locus of liver based on experiment of May 9, 1938.

Lungs.—In a number of experiments in which the pulmonary specific resistivity was measured, the lungs were rhythmically inflated in a manner which approximated normal ventilation before the chest was opened. Many sites on the lung surface from the hilar to more lateral regions and from apical to basal fields were explored. When the electrodes were inserted into the lung tissue, the resistances obtained were

entirely comparable to those obtained with the electrodes on its surface. Since the resistance of lung tissue varied from expiration to inspiration, the specific resistance was measured arbitrarily in most animals under conditions approximating the height of normal inspiration. The range of variation from normal expiration to normal inspiration was ascertained by holding the lung in an expiratory, and again in the maximal normal inspiratory, position until measurements could be made. When a series of measurements, over the range of frequencies used, was made with the electrodes in a given position on either the surface or in the depths of the tissue, and was then repeated immediately, there was practically no difference between the second and the initial series of measurements. This indicates that possible tissue changes due to placing of the electrodes did not have an important effect upon the final value for the resistance under these experimental

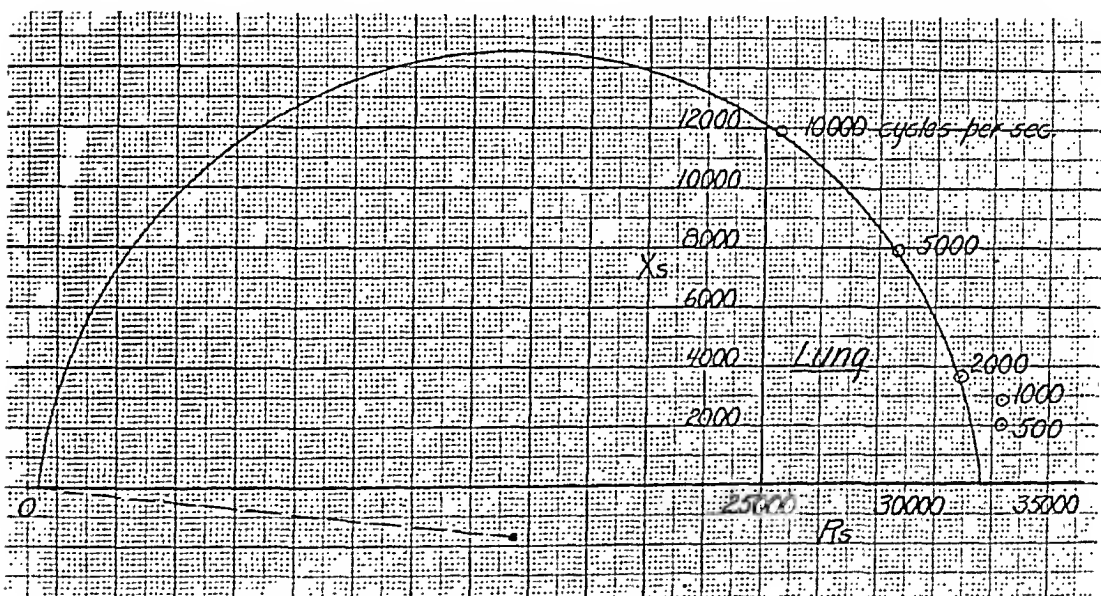


Fig. 5.—Impedance locus of lung based on experiment of May 9, 1938.

conditions. In a number of instances the lungs were overinflated until they were grayish-white in color, and bulged from the chest so that both expiratory and inspiratory volumes were greatly in excess of those possible in the living animal with an intact thoracic cage. The maximal resistance of the lung tissue of living animals under these conditions was about twice as great as that at the height of normal inspiration. When, however, death occurred suddenly with the lung at any volume, as a result of ventricular fibrillation induced by multiple air embolism of the smaller branches of the coronary arteries, the resistance of the rhythmically inflated lungs rose beyond the range of the measuring instruments.

Muscles.—The specific resistance of voluntary muscles (triceps, quadriceps, biceps, deep muscles of the back, intercostal muscles, recti, and diaphragm) was ordinarily studied after the fascial envelopes were incised. The measurements made on muscles included observations on the midportions, as well as on regions near the ends, where the connective tissue components became the more prominent constituents. The average resistance of muscle was not very different from that of normally inflated lung tissue. The specific resistance of the liver, as measured with the electrodes on the surface and in the depths of its substance, was nearly the same as that of muscle and lung tissue.

An attempt was made to measure the resistance of cardiac muscle during diastole. This was an especially difficult task when the heart was beating rapidly. The specific resistance of living cardiac muscle, with the electrodes either on the surface or imbedded, was found to be approximately one-third that of lung, muscle, and liver tissue, and about the same as that of blood. Fat and connective tissue had the highest resistances of any tissues measured. Bone and nerve were not studied.

The average values of the specific resistances of the various tissues are given in Table IV.

SUMMARY AND CONCLUSIONS

The specific resistances of living mammalian tissue *in situ* may be ascertained by measurement of the resistance between two small electrodes placed upon its surface or within its substance. The basis and scope of this method have been considered theoretically and verified by measurements of simple electrolytes and blood.

Measurements on the living tissues of the anesthetized dog show that muscle, normally inflated lung, and liver have specific resistances of the same order of magnitude. These measurements establish experimentally the validity of the assumption that the errors in theoretical studies of the form of the electrocardiogram, made by considering the tissues which surround the heart uniform with respect to their specific resistivity, are of no practical importance.

The writers wish to thank Dr. Frank N. Wilson for continued encouragement and valuable suggestions during the course of our work. We are grateful to Dr. A. L. Ferguson, of the Department of Chemistry, University of Michigan, who extended to us facilities in the Electrochemical Laboratory and helped us with some of our technical problems. We are particularly indebted to Dr. Kenneth S. Cole, of the Department of Physiology of the College of Physicians and Surgeons, Columbia University. It was he who suggested that point electrodes might be used for the measurement of tissue conductivities, and he was kind enough to provide the theoretical background of our problem. He also aided us on numerous occasions with advice and criticism. Without his assistance, this study could not have been possible.

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SHORT P-R INTERVAL WITH PROLONGED QRS COMPLEX: ALLERGIC MANIFESTATIONS AND UNUSUAL ELECTROCARDIOGRAPHIC ABNORMALITIES

REPORT OF A CASE

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THE following case in which the electrocardiogram showed a short P-R interval and a prolonged QRS complex in a healthy person who was subject to attacks of paroxysmal tachycardia is reported because there were unusual clinical and electrocardiographic features, several of which have not been reported previously.

REPORT OF CASE

A 24-year-old, well-developed, and somewhat obese man was admitted to the hospital with the chief complaint of attacks of rapid beating of the heart.

The family history was irrelevant except that one brother had hay fever caused by sensitivity to pollen and hair. The previous personal history was irrelevant except for morning sneezing.

The patient stated that he had been subject to attacks of rapid beating of the heart as long as he could remember, and that his mother told him he had had these seizures since birth. At the age of 10 years a physician told him not to engage in any strenuous sports. When he disregarded this advice and played a game such as baseball, a paroxysm was usually precipitated. Overexertion and fatigue increased the frequency of the attacks. In civil life, the seizures usually came on Saturday or Sunday, after a busy week, and averaged about one every three weeks. In the first four months that he was in the Army the paroxysms were more frequent, and were thought to have been precipitated by calisthenics or marching double time.

A typical attack began in the evening and was preceded by a period when the heart seemed to beat irregularly. The tachycardia started suddenly by the "heart jumping off its axis, giving a real hard knock, and then beating fast." During a paroxysm the patient felt dizzy, sweated profusely, and had a frontal headache. Seizures during the preceding eight months had been accompanied by pain in the chest, radiating to both shoulders. An attack necessitated the stopping of any activity and lying down. The paroxysm usually stopped as suddenly as it began, and left the patient weak and exhausted for a period of six to twelve hours. Attacks lasted from ten minutes to twelve hours. Occasionally there was a period of several hours before or after a seizure when the heart seemed to beat irregularly, but, between attacks, the patient felt perfectly well. Sometimes the patient was able to abort paroxysms by forced expiration with the glottis closed.

Physical examination revealed a well-developed and well-nourished young man who was seventy inches tall and weighed two hundred pounds. The cardiac examination was negative, as was the entire physical examination.

Laboratory examination, including roentgenographic and fluoroscopic examination of the heart, serologic reactions, blood cell count, and urinalysis, was negative.

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Allergic examination showed that the patient was sensitive to the following: chicken, mackerel, cane sugar, green pea, chocolate, barley, sweet corn, spinach, coffee, oyster, strawberry, horse serum, dust, goat epithelium, feathers, wool, fish glue, orris root, timothy, plantain, ragweed, ash, elm, *Aspergillus*, *Monilia*, trichophytin, and *Ascaris*. Passive transfer sites were tested with food allergens that produced moderate or greater reactions on skin testing, with the following results: cane sugar, green pea, and chocolate were markedly positive; mackerel and spinach were slightly positive.

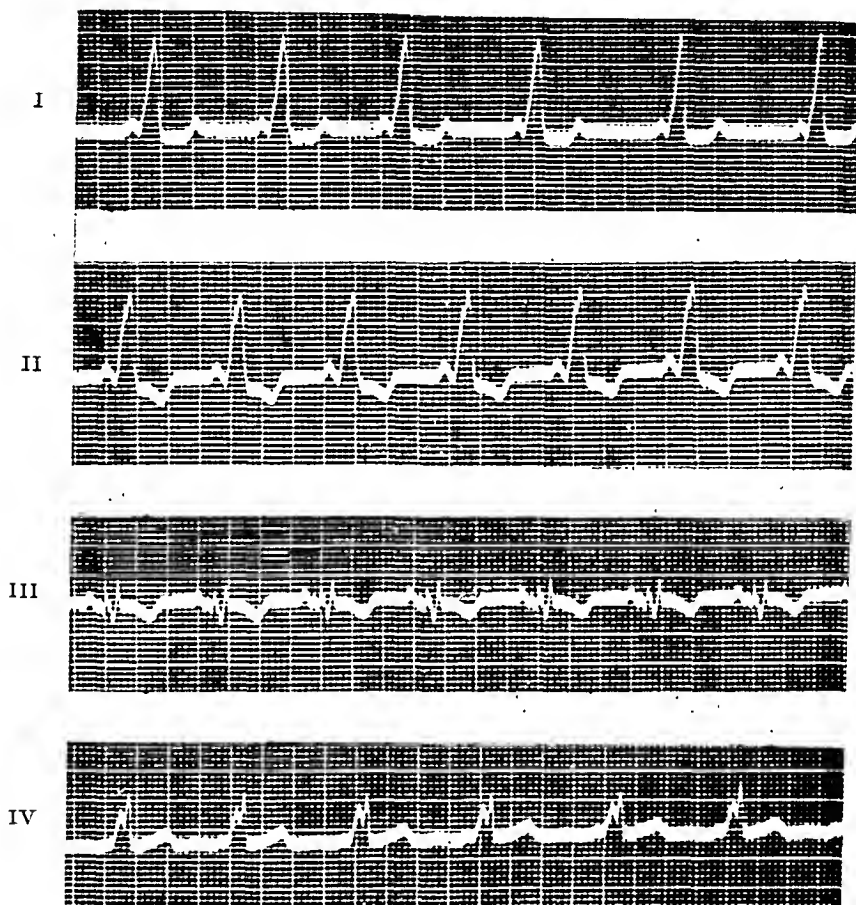


Fig. 1.

Electrocardiograms were obtained on this patient under many different conditions. These may be divided into several general groups, as follows:

The "normal" resting electrocardiogram (Fig. 1) showed a rate between 70 and 83, with slight sinus arrhythmia. The P-R interval was always 0.10 second. The QRS deflection was prolonged to 0.14 second, and the initial limb of this complex was slurred. The S-T segment was depressed in the limb leads, especially Lead II. The T wave was upright in Lead I and inverted in Leads II and III. The tracing was of the short P-R interval and prolonged QRS type which is associated with conduction through an accessory bundle, the bundle of Kent.

The tracing taken during an attack of tachycardia (Fig. 2) showed that the latter was supraventricular in origin, for the QRS deflection time was normal. The rate was about 180. The graph at the bottom of Fig. 2 is a strip of Lead II, taken during the attack while pressure was being applied to the carotid sinus. There are two normal complexes, the second of which has a P wave superimposed

on its S-T segment and is immediately followed by a ventricular complex which is transitional between the normal form and that present during the paroxysm. This process repeated itself several times, after which the tachycardia was resumed.

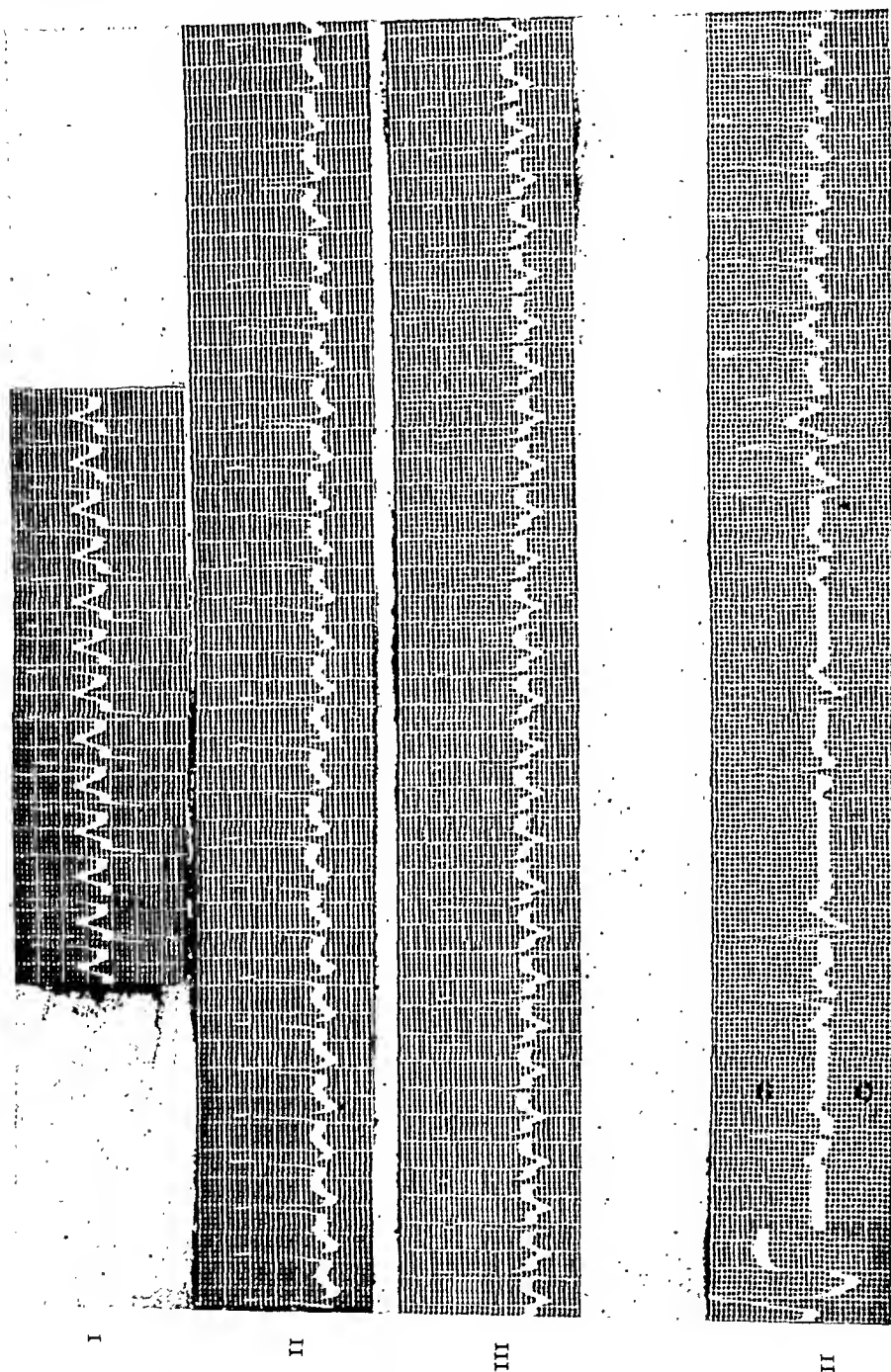


Fig. 2.

A tracing taken prior to his entry into this hospital (Fig. 3) showed a rate of 83 and an irregularity caused by premature beats. The prematurity was slight in Leads I and II, and more marked in Leads III and IV. In all leads except Lead III, there was a constant relationship between the complexes; that is, the normal

complexes were equally spaced, and so were the abnormal complexes. The normal complexes had a P-R interval of 0.18 second, a small Q_s , and an inverted T_s . The normal beats, therefore, were normal for a patient of his habitus (high diaphragm). The abnormal (premature) beats were similar to those in Fig. 1.

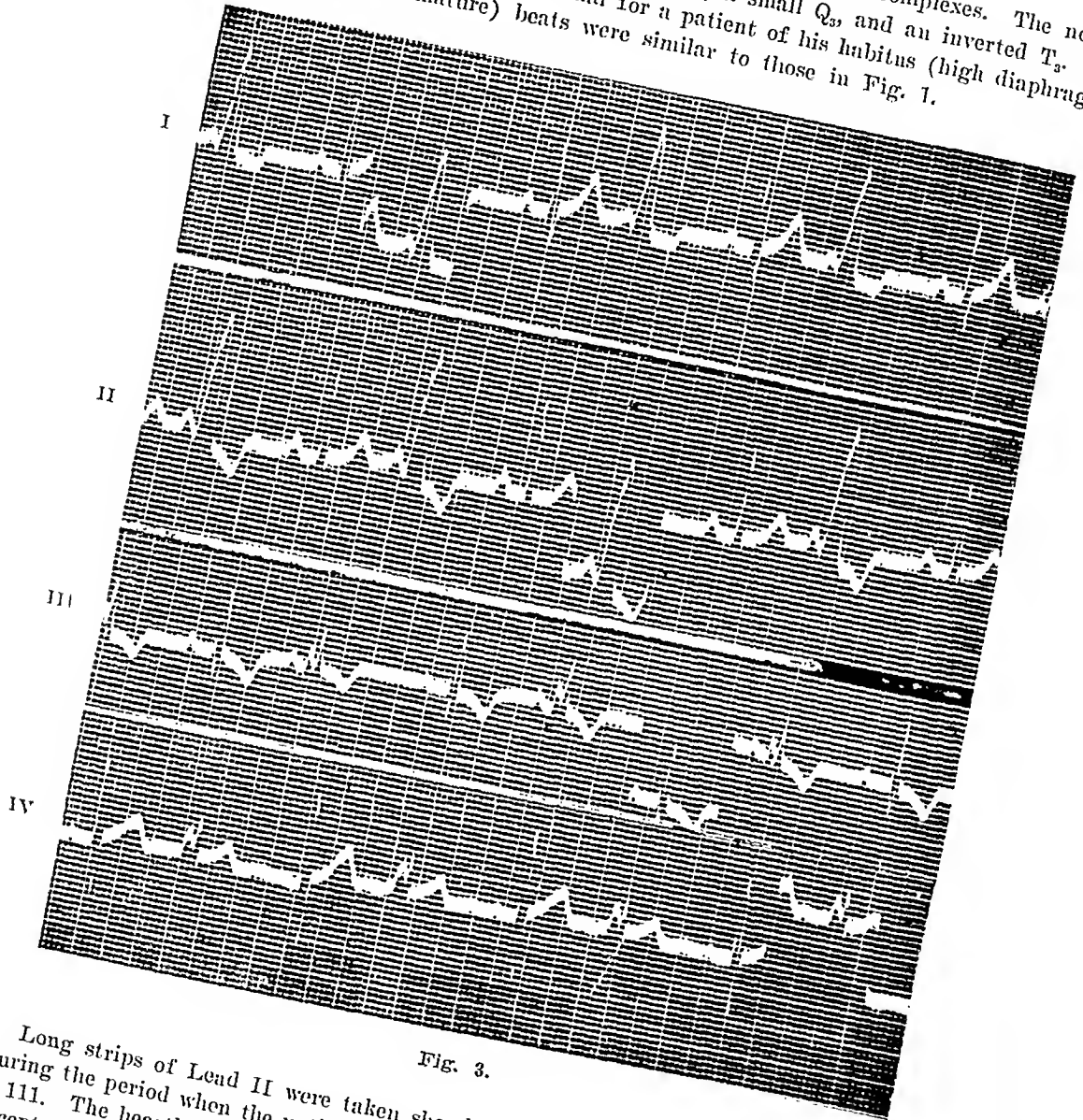


Fig. 3.

Long strips of Lead II were taken shortly before and after an attack (Fig. 4), during the period when the patient felt his heart beating irregularly. (A) The rate is 111. The heartbeat is regular, with normal and abnormal complexes alternating, except that the seventh abnormal complex is followed by two normal complexes. (B) The rate is 111. The heartbeat is regular, and two normal complexes alternate with an abnormal complex; all are equally spaced. (C) The rate is about 83. The heartbeat is irregular because normal and abnormal complexes alternate. Near the end of the strip, several abnormal complexes occur together. (D) The rate is 80 and the beating is irregular. Five normal complexes are followed by an irregular alternation of normal and abnormal complexes.

Strips of Lead II were taken on five occasions; the transition from "normal" rhythm to tachycardia is illustrated in the first four strips, and from tachycardia to "normal" rhythm in the last (Fig. 5). Fig. 5 A-D shows the result of carotid

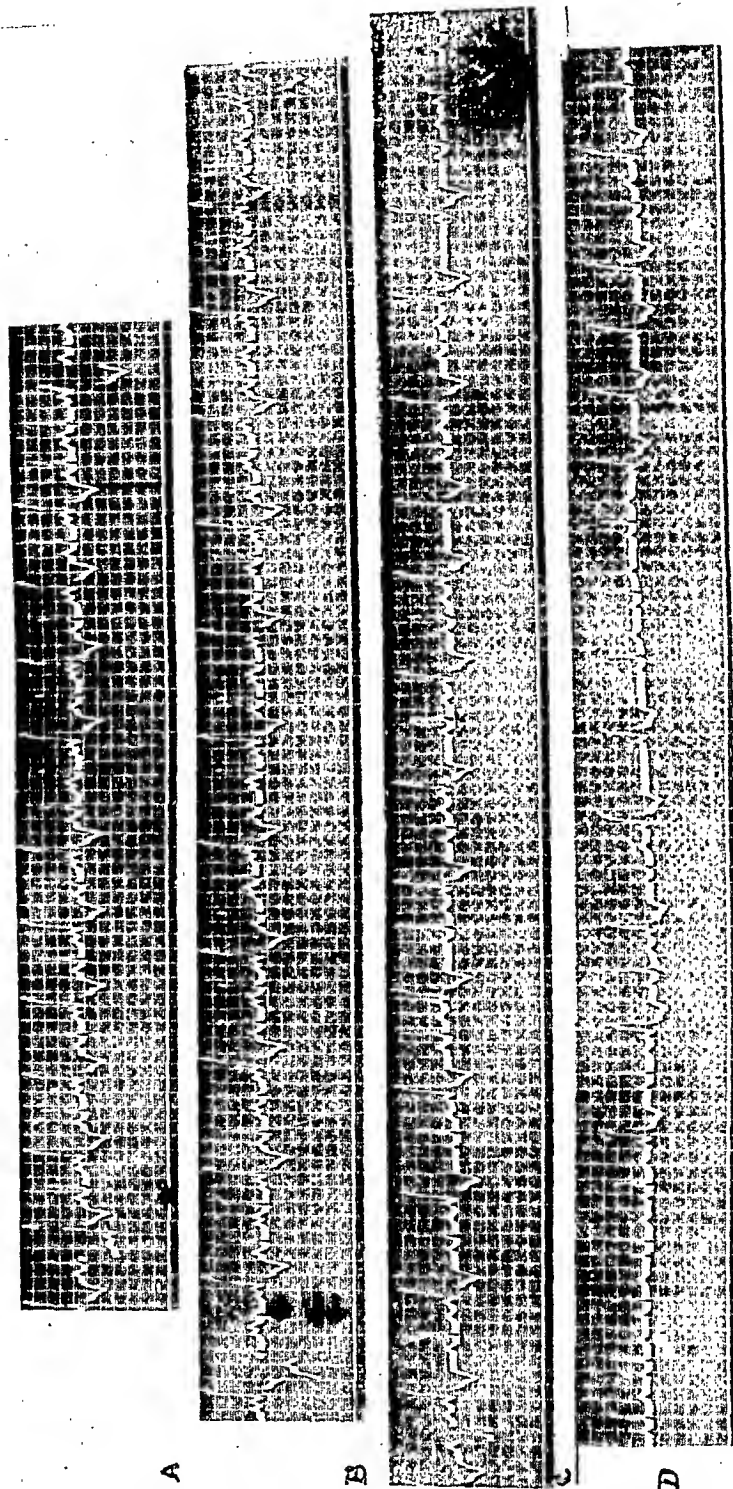


Fig. 4.—Strips of Lead II.

sinus pressure during an attack of tachycardia. Fig. 5 *A* shows what is probably the longest effect obtained by this procedure. In general, the effect of carotid sinus pressure lasted only a few beats before the tachycardia recurred. Fig. 5 *E* was taken just as an attack of tachycardia ended spontaneously.

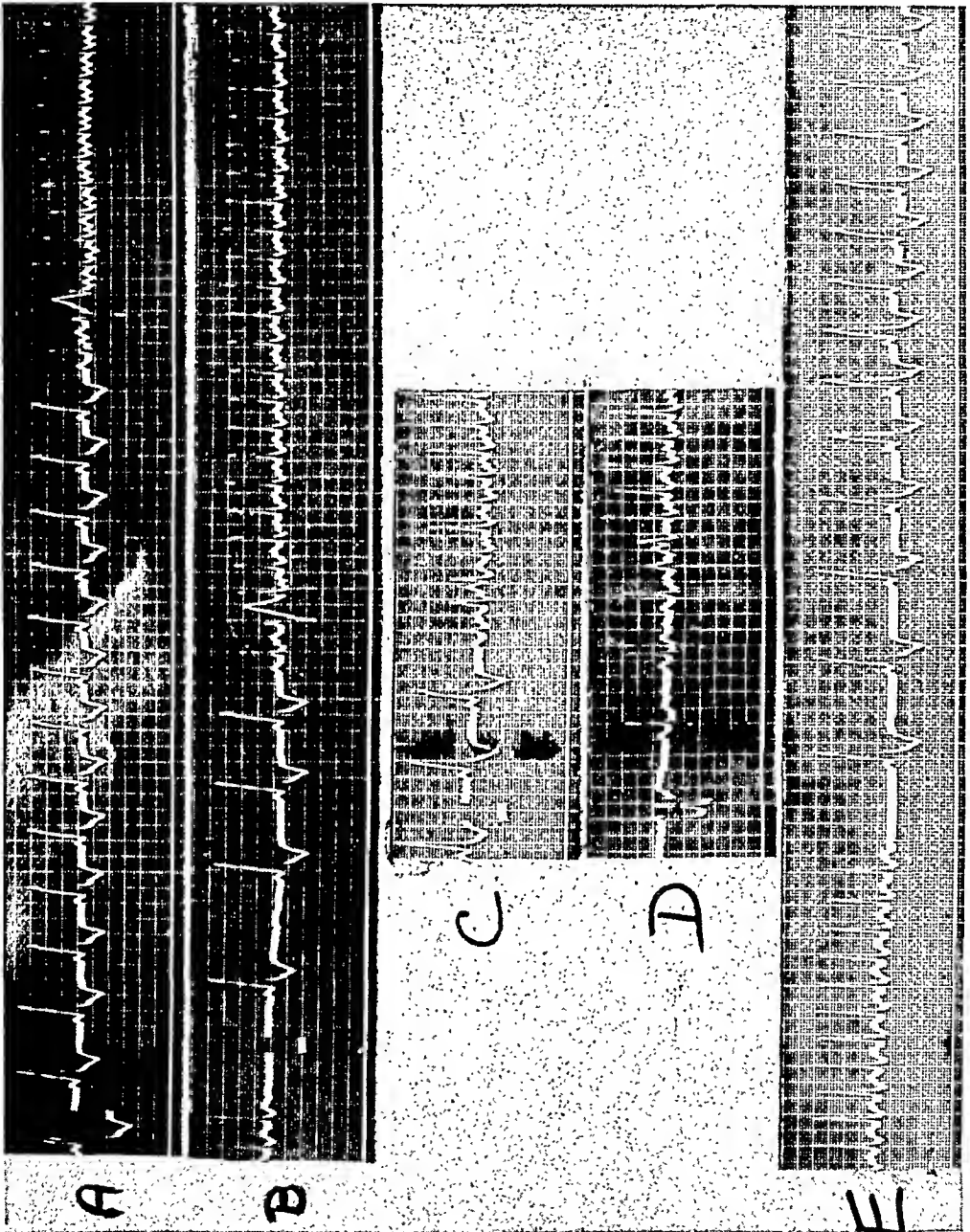


Fig. 5.—Strips of Lead II.

Tracings taken after exercise were essentially the same as in Fig. 1, except for an increase in rate. During ocular pressure (Fig. 6), the rate varied between 45 and 50 and there was a definite sinus arrhythmia. The tracing shows a lapse of 2.6 seconds between the first two complexes in Lead III. Note that the QRS complexes are of greater amplitude than those in Fig. 1; this increased amplitude makes the slurring less noticeable, but demonstrates that it involves only the initial component of the deflection. Tracings taken every five minutes after the administration of 1/50 grain of atropine sulfate were the same as that in Fig. 1, except

that the rate increased to about 90. With the increase in rate, the sinus arrhythmia became much less pronounced.

Progress.—Despite the physical rest provided by hospitalization, the patient continued to have attacks far more frequently than before; they occurred once, or sometimes twice, a week. Of the first four attacks, three occurred on Fridays, and the question was raised whether sensitivity to fish might be a precipitating factor. Consequently, fish was withheld on one Friday, but the patient had an attack on the same day after eating ice cream and drinking lemon soda. Several days later the patient was given fish for dinner but had no attack on that day.

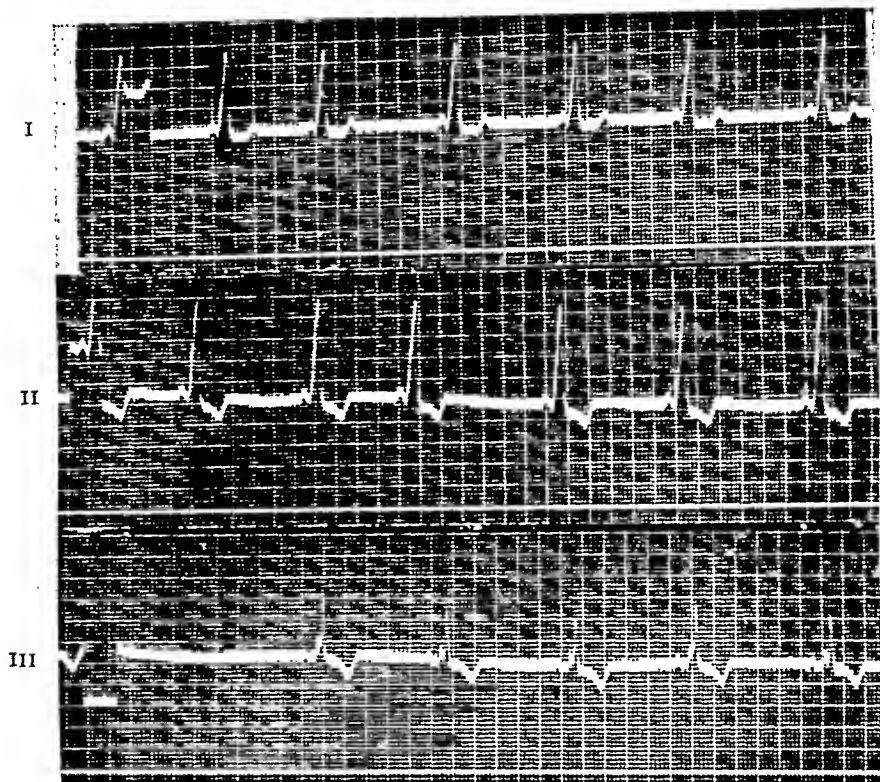


Fig. 6.

Subsequently, the patient was studied from the allergic standpoint. A list of substances to which he was sensitive has been given. He was then placed on a diet consisting only of lamb, rice, and milk for two days. On the third and fourth days, four teaspoonfuls of cane sugar were added twice daily. On the evening of the first day on which the sugar was given, the patient had an attack. The patient then was given nothing but lamb, rice, and milk for two more days. On the third day sugar was again added. This time, the patient noticed that his heart skipped irregularly on the first day the sugar was given, and that he had a definite attack on the second day. He was then placed on a full diet, except the foods to which he showed sensitivity. After several days on this diet, with no attacks, he left the ward, drank two bottles of a cola drink, and immediately had an attack. After explaining to the patient about the sugar content of soft drinks, he adhered rigidly to his diet and was more comfortable than at any time prior to his entrance into the hospital. He stated that he had never drunk soft drinks prior to hospitalization because he greatly preferred beer.

SUMMARY OF LITERATURE

Kent,¹ in 1914, published his observations, first made in 1892, on an accessory cardiac conduction bundle which crosses the auriculoventricular groove in the right lateral wall of the heart.

In 1915, Wilson² reported a case of mitral stenosis in which, during the course of a long period of observation, there were four different cardiac rhythms. When first observed (Wilson does not state whether the patient was febrile, nor does he give the pulse rate), the rhythm was normal. With slowing of the heart rate subsequent to deep breathing, a type of "bundle branch block" was found, together with a short P-R interval. Vagus pressure also caused this "block." Normal rhythm could be brought back by acceleration of the rate caused by $\frac{1}{50}$ grain of atropine or a succession of deep breaths. The patient had two attacks of paroxysmal tachycardia in six weeks. The fourth type of cardiac rhythm occurred during the early stage of atropine action (six minutes after injection), and was described by Wilson as a low nodal rhythm, in contradistinction to the other, or high nodal, type. He attributed these changes to migration of the pacemaker caused by vagus action.

In 1930, Wolff, Parkinson, and White³ described a syndrome of "bundle branch block with short P-R interval" in healthy young people who were prone to paroxysmal tachycardia, auricular fibrillation, or even auricular flutter. These patients usually regained normal rhythm spontaneously, either with exercise or by the action of atropine. These authors suggested the possibility of a congenital anomaly in the conduction system, but felt that the syndrome was probably the result of vagus action.

Holzman and Scherf⁴ and Wolferth and Wood,⁵ independently, presented the hypothesis that this syndrome is caused by an accessory pathway of auriculoventricular conduction. Wolferth and Wood presented the following reasons in support of their view: (1) The interval from the beginning of the P wave to the end of the QRS deflection is normal. (2) This interval was the same in the normal complex and the abnormal complex; a change occurred only in the P-R interval. (3) Slurring involved only the initial deflection of the QRS. They concluded that this was not bundle branch block, but the manifestation of an *early arrival* in the ventricle of the impulse from the auricle. They showed that a functioning bundle of Kent would account for all of the phenomena of this syndrome: (a) The P-R interval was short because the pathway was short. (b) Premature invasion of a section of the ventricular musculature would cause slurring of the initial deflection of QRS and widening of QRS at the expense of the P-R interval. (c) Conductivity through the bundle of Kent may be slow, so that it may fail to function when impulses are formed at a rapid rate. (d) Auricular paroxysmal tachycardia and fibrillation may be caused by retrograde conduction in the bundle, which was shown to occur in rats by Kent.

In 1936, Cossio, Berconsky, and Kreutzer⁶ advanced the theory that the abnormal complexes originate from a hyperirritable ventricular focus, and that this focus is irritated by the action of auricular systole.

In the same year, Tung⁷ presented two cases and expressed the opinion that the entire syndrome was the result of a change in vagal tone.

In 1937, Bishop⁸ reviewed the literature and found that the effect of atropine and exercise was not constant. This was evidence against the theory of vagus influence. The second theory, that of an aberrant conduction bundle, was discarded merely because such an anomaly had never been demonstrated in a patient with this syndrome.

In 1938, Moia and Inchauspe⁹ presented a case of this syndrome and noted absence of Q in Lead IV (old technique), absence of axis deviation, and T waves in a direction opposite to QRS. A strip of Lead II showed abnormal complexes with occasional normal beats; there was coupling for several beats, but no regular bigeminy.

In 1940, Hunter, Papp, and Parkinson¹⁰ reviewed this subject and suggested that the abnormal complexes may be explained as the result of double rhythm by two interfering pacemakers.

In 1941, Wolferth and Wood¹¹ re-examined this subject and presented further evidence in support of their original hypothesis.

In 1942, Butterworth and Poindexter¹² reported two cases in which auricular premature beats were followed by abnormal ventricular complexes. This was in refutation of several theories, especially that of double rhythm caused by two interfering pacemakers. They also presented experimental work in which, by means of an amplifier, the electrical impulses from the auricle were conducted to the ventricle *before* the impulse arrived normally through the auriculoventricular conduction system. This produced typical electrocardiographic tracings, with short P-R interval and prolonged QRS complexes. Reversal of the flow, from ventricle to auricle, caused typical auricular tachycardia. This demonstration lent weight to the theory of Wolferth and Wood regarding retrograde conduction in the bundle of Kent as a cause of the paroxysms of auricular tachycardia.

Wood, Wolferth, and Geckeler,¹³ in 1943, obtained an autopsy on a patient who had had this syndrome. They found an accessory bundle exactly where it was described by Kent.

In 1925, it was realized that paroxysmal tachycardia occurred with certain other diseases too often to be considered merely coincidental. Laubry and Mussio-Fournier¹⁴ reported seven cases of both asthma and paroxysmal tachycardia; Thomas and Post¹⁵ wrote of the frequent occurrence of paroxysmal tachycardia in cases of migraine, and suggested that the tachycardia might be an unusual manifestation of this disease.

It was not until four years later that Luria and Wilensky¹⁶ first postulated that paroxysmal tachycardia is an allergic disease. The following year, they¹⁷ presented the case of a woman with mitral valvular disease who was subject to attacks of paroxysmal tachycardia. These

attacks would occur immediately after eating raisins and honey. Skin tests with apple, starch, raisin, and honey showed positive reactions to raisin and honey. Elimination of these foods from the diet resulted in cessation of the attacks.

In 1932, Weill¹⁸ referred to the work of Luria and Wilensky¹⁷ and reported six cases in which paroxysmal tachycardia was associated with asthma, urticaria, and other allergic phenomena. He stated that paroxysmal tachycardia was not always allergic, but felt that allergy was a definite factor in some cases. One patient had migraine, eczema, and paroxysmal tachycardia. She ate chocolate constantly while working, and consumed an enormous quantity. Upon the removal of chocolate from her diet, the attacks of migraine and tachycardia almost, but never completely, disappeared.

In the same year, Mussio-Fournier¹⁹ referred to his original article and presented further evidence in favor of the idea that allergy may be a factor in paroxysmal tachycardia.

In 1937, Gay²⁰ referred to cases in which paroxysmal tachycardia was controlled by eliminating certain foods from the diet; the tachycardia recurred when these foods were again eaten.

Kern²¹ stated that paroxysmal auricular tachycardia is perhaps the most outstanding cardiac disorder in which allergy may play a part.

DISCUSSION

This case is presented because of the unusual electrocardiograms, the unusual reaction to exercise, and the possibility that the precipitation of the paroxysmal tachycardia might have been an allergic manifestation.

ELECTROCARDIOGRAMS

1. With a slow rate, there was marked sinus arrhythmia, all of the complexes were abnormal, and the QRS complexes were of greater amplitude and less slurred than when the rate was more rapid.

2. With increase in rate after exercise or atropine, the typical patient with this syndrome would show a return to normal rhythm, but in this case it was impossible to produce a single normal complex by causing an acceleration of the rate. When the rate was increased to over 90, the sinus arrhythmia disappeared. The QRS complexes were of lower voltage and the notching was more evident.

3. With the fast rate preceding or following an attack of paroxysmal tachycardia, normal complexes were frequently seen together with abnormal complexes; in none of the tracings were all of the complexes normal. The mechanism of these changes is highly problematical, and will not be discussed in this paper, except to say that, when bigeminy was present, it was evident that the cardiac impulses alternated between the normal bundle and the bundle of Kent. From the practical standpoint, it should be noted that the tracing in Fig. 3 showed a constant

bigeminal rhythm.* If this were the only tracing available, one could not be criticized for failing to make the correct diagnosis. This should teach us that multiple tracings are required whenever the underlying mechanism is not perfectly clear.

4. It is interesting that the only time normal complexes occurred was immediately before or after a paroxysm of tachycardia. With the theory of Wolferth and Wood and the experimental evidence of Butterworth and Poindexter in mind, might this not mean that an occasional *normal* complex initiates an impulse which re-enters the auricle through the bundle of Kent and there sets up a paroxysm of tachycardia?

5. In cases of typical supraventricular paroxysmal tachycardia, carotid sinus pressure, if effective at all, will cause the tachycardia to disappear entirely. Such was not the case in this patient; sustained pressure caused the tachycardia to cease for several beats, after which it was resumed.

ALLERGIC STUDY

1. Inasmuch as the syndrome of short P-R interval and prolonged QRS complex, associated with paroxysms of tachycardia, is well recognized, it seems far fetched to look upon allergy as a cause of these attacks.

2. I have seen one patient with this syndrome (discovered on routine examination) who regained normal rhythm after exercise and had never had an attack of tachycardia.

3. Although allergy is probably not always a factor in this syndrome, it is reasonable to suppose that it may act as a precipitating cause of some of the paroxysms of tachycardia which these patients have. This particular patient had about one attack every three weeks prior to his entrance into the hospital. When he began to drink soft drinks instead of beer, he had attacks much more often. His skin tests (and passive transfer reactions) showed strong reactions to cane sugar and a few other common foods. On two occasions, after the patient had been on a diet of lamb, rice, and milk, the addition of cane sugar was followed by an attack. When the patient was placed upon a diet which eliminated all foods to which he was sensitive, the attacks became less frequent and the patient was much more comfortable.

4. It is hoped that this report will serve to stimulate interest in the possible allergic aspects of this syndrome.

SUMMARY

1. A case in which the electrocardiogram showed a short P-R interval and a prolonged QRS complex, together with several unusual features not reported previously, is presented.

Thorough search of the literature failed to reveal any publication or description of such a tracing. The only similar record is one published by Moia and Inehauspe, which differed in that it never showed regular alternation or a constant bigeminal rhythm. Alternation between normal and bundle branch block complexes should not be confused with this type of tracing.

2. The possibility that food allergy may have precipitated some of the attacks of paroxysmal tachycardia is considered.

The study of this case from the allergic standpoint was conducted by Lieutenant Harry Swartz.

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THE PERIPHERAL BLOOD FLOW UNDER BASAL CONDITIONS IN NORMAL MALE SUBJECTS IN THE THIRD DECADE

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THERE has been increasing interest in recent years in that part of the total cardiac output which is allocated to the peripheral circulation. Contributions to our knowledge of peripheral blood flow have been stimulated by increasing attention to inflammatory, occlusive, and vasospastic states of the peripheral vessels. Most of the data relating to the amount of the peripheral circulation have been derived from changes in the volume of an extremity or digit, or in the temperature of an extremity. During the past four years we have used a method by which measurement of the amount of blood allotted to the periphery of the body can be made in health and disease, as well as to estimate the effect of drugs on this part of the circulation.¹⁻⁷ During the course of these investigations we have accumulated data on the average peripheral blood flow in a group of normal persons between the ages of 20 and 30 years.

The peripheral blood flow has now been studied seventy-five times on thirty-four male subjects who, from physical examination, could be designated as normal. All were approximately 20 to 30 years of age, and most of them were members of the house staff of the New York Hospital or medical students from Cornell University Medical College.

METHOD

Measurements of the peripheral blood flow were made by modifying the method of Hardy and Soderstrom⁸ in such a way that observations could be carried out without the use of a calorimeter. This modification has been described elsewhere.^{1, 2, 6} In order to use this method, certain data were required, namely, skin temperatures at eleven points on the anterior surface of the body,¹ rectal temperature, oxygen consumption, height, and body weight. In addition, the blood pressure and pulse rate were recorded.

The skin temperatures were measured with the improved Hardy-Soderstrom radiometer,⁹ the rectal temperature with a single-junction, copper-constantan thermocouple,⁹ and the oxygen consumption with a Benedict-Roth metabolism apparatus.¹⁰ The basal metabolic rate was calculated from the Mayo Foundation standards for age and sex,¹¹ and the surface area from the tables of DuBois and DuBois.¹²

PROCEDURE

All of the observations were made in the morning, when the subjects were in a basal metabolic state. The rectal thermometer was inserted to a depth of about 10 cm. as soon as the subjects came to the constant temperature room, and remained in place throughout the morning. The subjects lay nude in bed covered

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only by a sheet. The studies were made at the temperatures which we have most frequently employed, namely, 25° C. and 27° C. The relative humidity was maintained between 30 per cent and 50 per cent. The subjects adjusted to the environment of the constant temperature room for at least an hour before the observations were begun.

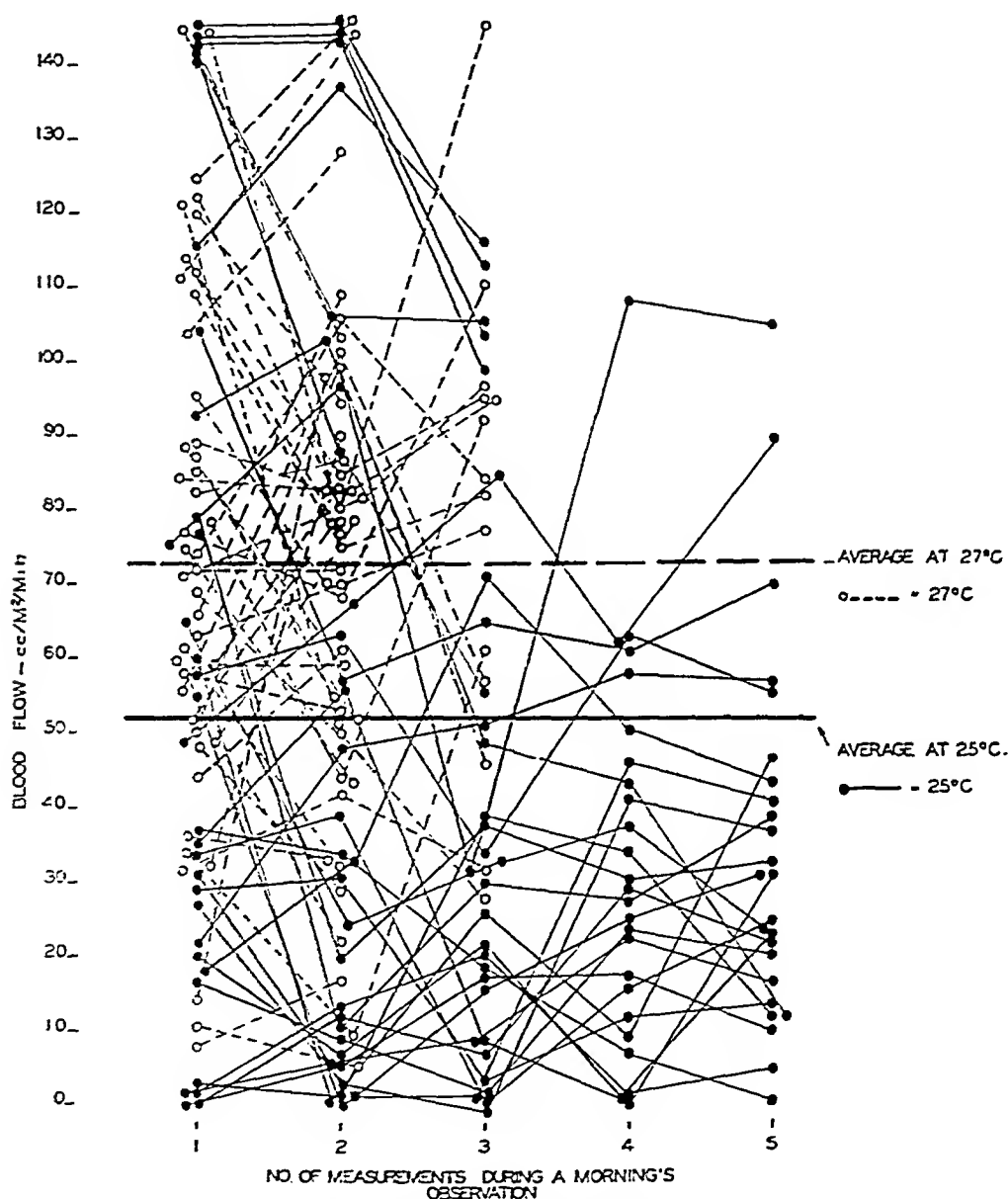


Fig. 1.—This figure shows all of the individual measurements of average peripheral blood flow on all subjects during the course of a morning's observations. Those made at a room temperature of 25° C. are plotted as closed circles, and those at a room temperature of 27° C. are shown as open circles. For the most part, the peripheral blood flow was greater at the higher room temperature.

The data were collected in the following order: First, the oxygen consumption was measured. The room temperature was then noted, after which the temperatures of the skin of the eleven areas were recorded. The rectal temperature was next measured. Six sets of skin and rectal temperatures were recorded on some subjects, and three to four sets on others. The interval between temperature readings was ten minutes in some cases and twenty minutes in others. The average peripheral

blood flow per minute during the ten- or twenty-minute intervals was calculated, and is shown in Fig. 1. This flexibility was permissible, for the final calculations of peripheral blood flow were made on the basis of c.c./M²/Min. The blood pressure and pulse rate were recorded during free intervals between temperature readings. After obtaining the required number of sets of skin and rectal temperature, the oxygen consumption was measured again.

OBSERVATIONS

The results of observations at a room temperature of 25° C. are shown in Table I, and those at 27° C. in Table II.

Peripheral Blood Flow.—The trends of the peripheral blood flow during the course of a morning's observation are shown in Fig. 1. During an observation, the peripheral blood flow in any one subject showed fluctuations. Also, in successive observations on the same subject, a variation was observed. Although there is overlapping in values at the two temperatures, nevertheless it is apparent that, for the most part, at 27° C. the peripheral blood flow was greater than at 25° C. In one subject (No. 25, G. V., Table I), the peripheral blood flow with the room temperature at 25° C. was, on the six occasions when it was measured, 97 to 163 c.c./M²/Min.—that is to say, greater than all the others of this group, in which the next highest was 78 c.c./M²/Min. The basal metabolic rate was consistently in the lower range. We have no explanation for the fact that this subject's peripheral blood flow was so far out of line with the others in this group.

In two subjects (No. 8, M. McC., and 11, W. L., Table II), at the higher room temperature (27° C.), the peripheral blood flow was much less than that of all of the others of this group. Their basal metabolic rates were in the low range, but others in the group with lower basal metabolic rates had a greater peripheral blood flow, so that this is probably not the explanation for their low values.

In four subjects (No. 1, L. E., 6, R. T., 12, C. H., and 13, J. S., Table II, and subjects No. 5, L. E., 1, R. T., 22, C. H., and 7, J. S., Table I, respectively), the peripheral blood flow was measured at 27° C. as well as at 25° C., and was greater at the higher room temperature.

The average peripheral blood flow for all subjects was 52 c.c./M²/Min. at a room temperature of 25° C., and 73 c.c./M²/Min. at a room temperature of 27° C. That is to say, the peripheral blood flow was 21 c.c./M²/Min. greater at the higher room temperature (Tables I and II).

Basal Metabolism.—The average basal metabolic rate at 25° C. was minus 6 per cent. In this group the highest basal metabolic rate was plus 15 per cent, and the lowest, minus 18 per cent (Table I). The average at 27° C. was minus 5 per cent. The highest basal metabolic rate in this group was plus 20 per cent, and the lowest, minus 23 per cent (Table II). When more than one set of observations was made on a subject, slight variations in oxygen consumption were observed from day to day (Tables I and II). Approximately 60 per cent of the

TABLE I
DATA RELATING TO 25 NORMAL MALE SUBJECTS AT A ROOM TEMPERATURE OF 25° C.

SUBJECT NUMBER	DATE	PERIPHERAL BLOOD FLOW C.C./M ² /MIN.	AVERAGES OF					PULSE RATE PER MIN.
			BASAL METABOLIC RATE %	RECTAL TEMP. °C.	SKIN TEMP. °C.	HAND TEMP. °C.	FOOT TEMP. °C.	
1. R. T.	6/10/41	23	-14	36.49	32.19	32.9	28.9	61
2. J. S.	6/11/41	71	+4	36.53	33.17	34.1	33.9	73
3. A. R.	6/12/41	47	0	36.82	33.21	33.8	29.9	60
4. F. E.	6/18/41	14	-12	36.60	32.41	32.6	27.7	59
5. L. E.	6/20/41	36	-5	36.73	32.72	33.6	30.4	48
6. L. L.	2/21/41	22	+15	37.26	32.84	33.3	28.4	64
7. J. S.	6/23/41	38	-11	36.85	33.26	34.5	33.6	68
8. R. M.	6/24/41	18	-9	36.42	32.75	33.9	31.5	48
9. F. McN.	6/26/41	19	-18	36.58	32.74	32.7	30.9	65
10. A. P.	6/27/41	8	-18	36.87	32.43	33.6	28.8	52
11. W. McD.	6/28/41	55	-1	36.65	33.23	34.6	33.4	68
12. B. V.	6/30/41	39	+1	36.90	32.98	33.3	29.6	56
13. G. D.	7/ 5/41	14	-5	36.71	32.86	34.4	32.7	64
14. C. L.	7/ 9/41	14	-4	37.07	32.53	32.8	27.1	56
15. R. O.	7/10/41	10	-1	37.06	32.68	33.2	28.1	61
16. T. R.	7/11/41	18	-12	36.63	32.89	33.8	32.6	63
17. J. B.	7/12/41	11	-17	36.60	32.71	33.9	31.9	56
18. A. M.	7/30/41	26	-7	36.37	32.39	33.6	30.2	60
19. S. H.	7/16/41	28	-11	36.77	32.41	33.1	31.5	52
20. J. F.	7/17/41	24	-3	36.84	32.79	32.8	30.0	65
21. C. S.	7/29/41	84	+5	36.55	33.39	34.3	32.7	47
22. C. H.	7/21/41	37	-5	36.66	32.92	34.2	32.4	58
23. K. D.	7/25/41	43	-5	36.62	33.22	34.0	33.2	60
24. T. H.	7/15/41	78	+11	36.76	33.32	34.0	32.8	56
	7/19/41	51	+3	36.72	32.40	32.9	30.6	56
25. G. V.	2/17/42	119	+3	36.43	33.50	33.5	33.0	48
	2/18/42	97	-11	36.24	33.79	33.9	32.5	49
	2/19/42	163	-18	36.28	34.08	34.3	33.7	52
	2/21/42	122	-6	36.11	33.77	34.5	33.9	52
	3/10/42	134	-12	36.42	33.76	34.2	33.5	48
	3/12/42	140	-14	36.44	33.90	34.8	34.0	56
Group Averages		52 c.c.	-6%	36.64° C.	33.01° C.	33.7° C.	31.4° C.	57

subjects in both groups showed a slight increase in basal metabolic rate during a morning's observations, and 40 per cent showed a decrease. This is not apparent in Tables I and II, however, in which the average rate for the morning's experiment is recorded.

Rectal Temperature.—The average rectal temperature with the room at 25° C. was 36.64° C., and, at 27° C., it was 36.79° C.; that is to say, it was slightly higher at the higher room temperature (Tables I and II). The lowest rectal temperature with the room at 25° C. was 36.11° C., and the highest, 37.26° C. (Table I). At 27° C. the lowest rectal temperature was 36.32° C., and the highest, 37.24° C. (Table II). Small variations in rectal temperature were observed from day to day among those subjects upon whom several measurements were made (Tables I and II).

Skin Temperature.—The average skin, hand, and foot temperatures with the room at 25° C. were 33.01° C., 33.7° C., and 31.4° C., respectively (Table I). The average skin, hand, and foot temperatures at 27° C. were 33.75° C., 34.4° C., and 32.7° C., respectively (Table II). In short, the skin temperatures were higher at the higher room temperature. When more than one set of observations was made on a subject in either group, the average skin, hand, and foot temperature varied from day to day. The highest average foot temperature was recorded at the highest room temperature (E. B., 3/2/42; F. H., 9/29/41; and R. T., 10/30/41, Table II). On the other hand, the lowest individual average foot temperature (26.0° C.) was recorded at the higher room temperature (R. B., 1/21/41, Table II). The highest and lowest individual average skin and hand temperatures were always greater at the higher room temperature.

Blood Pressure and Pulse Rate.—The average systolic and diastolic blood pressures were the same at 25° C. as at 27° C. There was a slight difference in average pulse rate, which was 57 per minute at 25° C. and 61 per minute at 27° C. (Tables I and II). Neither the blood pressure nor pulse rate varied significantly from day to day in any one subject (Tables I and II).

DISCUSSION

The average peripheral blood flow was 52 c.e./M²/Min. with the room temperature at 25° C., and 73 c.e./M²/Min. at 27° C. (Tables I and II, Fig. 1). That is to say, the average peripheral blood flow bears a direct relationship to environmental temperature, for the blood flow was 21 c.e./M²/Min. greater at the higher room temperature. These results are in agreement with those of Hardy and Soderstrom⁸ and Hick, Keeton, Gliickman, and Wall.¹³ However, when each individual in each group was considered, the variation in blood flow was such that values for certain subjects at one temperature overlapped those at the other (Tables I and II, Fig. 1). In addition, when several observations were carried out on a subject, the peripheral blood flow varied from one day

TABLE II
DATA RELATING TO 14 NORMAL MALE SUBJECTS AT A ROOM TEMPERATURE OF 27° C.

SUBJECT NUMBER	DATE	PERIPHERAL BLOOD FLOW C.C./M ² /MIN.	AVERAGES OF						PULSE RATE PER MIN.
			BASAL METABOLIC RATE %	RECTAL TEMP. °C.	SKIN TEMP. °C.	HAND TEMP. °C.	FOOT TEMP. °C.	BLOOD PRESSURE MM. HG.	
1. L. E.	9/10/41	87	-10	36.64	33.77	34.1	32.4	105/64	55
	11/16/41	72	-13	36.55	33.80	34.2	33.3	112/61	43
	1/ 9/42	56	-10	37.00	34.16	34.4	32.8	105/60	50
	5/19/42	71	-5	36.80	33.75	34.4	33.7	102/62	53
	2/24/42	70	-4	36.89	33.90	34.6	33.5	101/68	69
2. E. B.	2/26/42	49	-10	37.15	33.79	34.9	33.9	107/80	69
	3/ 2/42	119	+2	37.02	34.21	35.0	34.3	102/72	71
	3/ 3/42	85	0	37.07	33.86	34.8	34.2	106/73	70
	3/ 4/42	67	+5	36.74	33.80	34.6	34.0	109/70	60
	3/ 7/42	97	+12	36.36	33.28	34.1	33.8	106/70	62
3. R. B.	3/18/42	69	-12	36.93	33.94	34.6	34.2	102/68	66
	1/21/41	39	+1	37.10	33.41	33.8	26.0	106/70	60
	3/21/42	89	+3	37.24	33.71	34.5	28.9	106/71	65
	5/23/42	35	-10	36.86	33.06	33.9	29.6	100/70	62
	8/ 6/41	82	0	37.09	33.38	34.1	31.5	121/81	71
4. W. S.	1/ 3/42	93	-10	36.61	33.66	34.3	33.0	114/73	71
	2/12/42	83	-12	36.32	32.65	32.8	32.5	111/75	55
	5/20/42	35	-15	36.60	33.34	34.1	33.2	105/71	54

5.	F. H.	9/5/41	77	-3	36.79	33.87	34.6	33.5	142/67	56
		9/29/41	54	+1	36.75	33.84	35.1	34.3	103/69	61
		10/27/41	72	+1	36.48	33.36	34.3	33.5	95/69	42
		11/15/41	46	-2	36.81	33.67	34.6	32.9	94/62	59
		12/5/41	113	+2	36.91	34.05	34.3	33.0	101/68	64
		12/6/41	157	+5	36.68	33.91	34.5	33.8	106/70	61
		12/9/41	71	-6	36.48	33.83	34.7	33.9	109/71	59
		12/18/41	41	+8	37.01	33.15	34.4	33.6	103/69	56
		1/3/42	41	-5	36.92	33.28	34.2	33.8	103/71	59
		1/12/42	67	-1	36.86	33.71	34.9	34.2	101/69	56
		2/1/42	91	+4	36.92	34.00	34.9	34.2	103/67	61
6.	R. T.	10/28/42	60	-19	36.38	33.70	34.7	34.2	114/73	65
		10/30/41	108	-10	36.61	33.82	34.8	34.3	108/69	59
		11/11/41	86	-18	36.61	33.93	34.7	34.0	111/70	60
7.	F. D.	9/11/41	61	-13	36.73	33.77	34.0	32.6	103/70	57
		9/30/41	126	-6	36.69	34.26	34.6	33.8	109/74	57
		10/22/41	116	-5	36.87	34.18	34.6	34.1	107/73	60
8.	M. McC.	9/18/41	13	-23	36.87	33.37	33.5	31.8	101/64	60
		2/22/42	87	-19	36.79	33.50	34.0	28.6	97/58	65
		2/25/42	83	-19	36.79	34.25	33.8	29.5	96/65	59
9.	G. W.	10/29/41	31	0	36.77	33.80	33.3	29.6	105/63	54
10.	R. B.	1/25/41	134	+20	36.86	34.35	34.3	32.5	105/73	76
11.	W. L.	10/31/41	8	-2	36.98	33.25	33.2	27.3	108/77	67
12.	C. H.	1/21/41	63	-8	36.81	34.25	35.1	34.2	99/66	64
13.	J. S.	2/1/41	56	-16	36.57	34.36	34.8	33.9	107/71	64
14.	W. B.	12/30/41	71	-1	36.95	34.18	33.5	29.6	97/65	61
Group Averages			73 c.c.	-5%	36.79° C.	33.79° C.	34.1° C.	32.7° C.	105/71	61

to the next (Tables I and II, Fig. 2*a* and 2*b*). Although there were variation and overlapping in values, the peripheral blood flow tended for the most part to be greater at the higher room temperature (Fig. 1). These data show, therefore, that the peripheral blood flow did not lie within narrow limits, among different subjects in the same age and temperature group, or in the same person. This was not unexpected, for, although all of the observations were made under the same conditions, many factors, such as emotion, metabolic requirements of the tissues, and the amount of subcutaneous fat, determine how much of his total basal cardiac output each person must allot to the periphery.

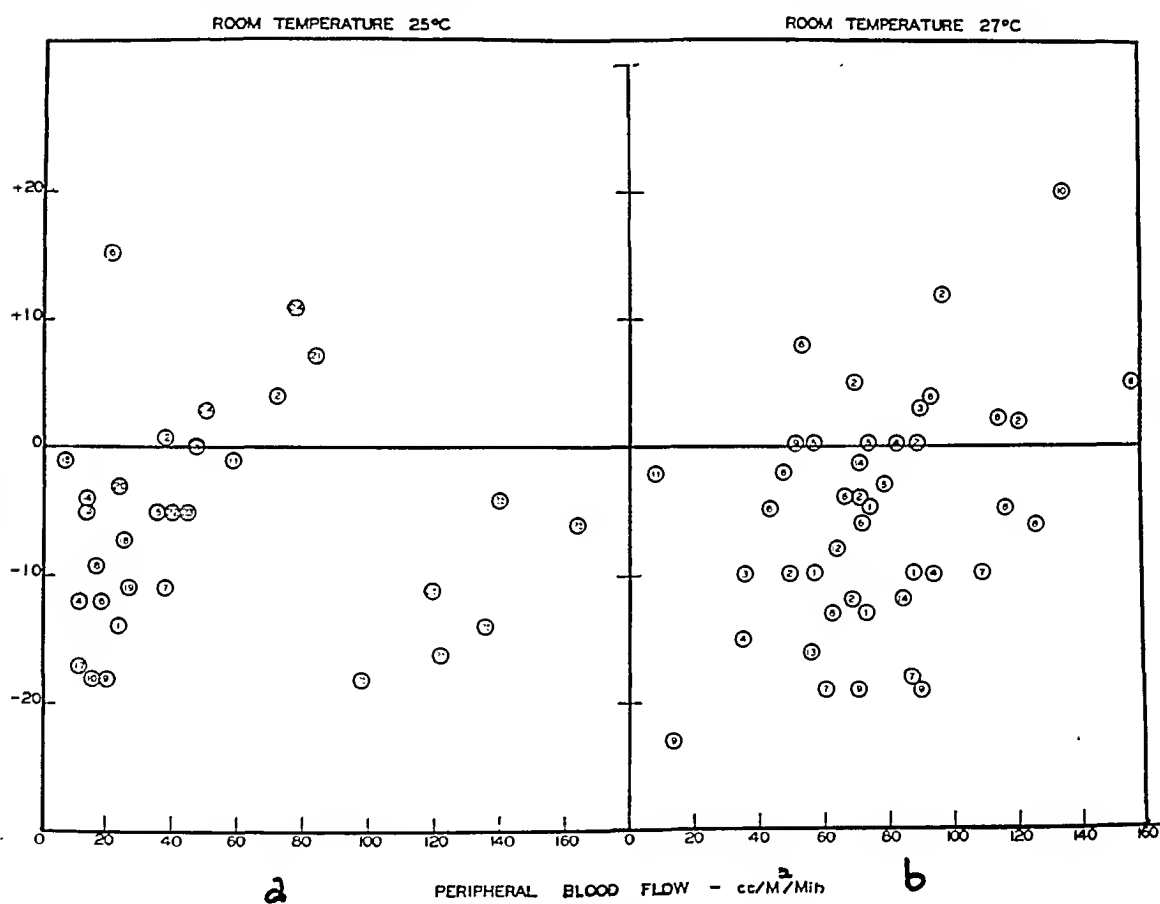


Fig. 2.—In this figure the data for peripheral blood flow are plotted against the corresponding basal metabolic rates at 25° C. and 27° C., respectively. A linear relation is established, for with an increase in basal metabolic rate the peripheral blood flow also increases. The numbers in the circles refer to subjects in Tables I and II. In the observations made at 25° C. we have no explanation for the dislocation of subject 25 from the rest of the group.

The average basal metabolic rate was the same for both groups of subjects; that is to say, it was minus 6 per cent at 25° C. and minus 5 per cent at 27° C. (Tables I and II). The highest and lowest basal metabolic rates in the two groups were essentially the same, i.e., plus 15 per cent and minus 18 per cent, respectively, at 25° C., and plus 20 per cent and minus 23 per cent, respectively, at 27° C. (Tables I and II). When more than one set of observations was carried out on

one subject, small variations in basal metabolism were observed from day to day. Approximately 60 per cent of the measurements in both groups showed small increases in oxygen consumption at the end of a morning's observation, and 40 per cent showed small decreases in basal metabolic rate. This is not apparent in Tables I and II because they show the average of all the basal metabolic rates for the morning's experiment. Benedict and Campbell¹⁴ were unable to detect from their data on a large number of subjects any definite change in oxygen consumption during a morning's observation. Furthermore, DuBois¹⁵ could find no consistent change in basal metabolism during the day. Although our subjects lay quietly in the basal metabolic state, certain observations were being made upon them, i.e., skin temperatures were taken over the anterior surface of the body at certain intervals and blood pressures and pulse rates were recorded. The tendency for the oxygen consumption to increase slightly in 60 per cent of the measurements during a morning's observation was probably of no significance. On the whole, there was a rough linear relationship between the amount of peripheral blood flow and basal metabolic rate, for, at both 25° C. and 27° C. room temperature, there was a gradual increase in peripheral blood flow from those with the lower basal metabolic rate to those with the higher metabolic rate (Fig. 2a and 2b). This relationship between basal metabolic rate and peripheral blood flow was much more apparent in the patients with myxedema¹⁶ and hyperthyroidism¹⁷ who were studied by Stewart and Evans (Fig. 2a and 2b).

The group averages of rectal, skin, hand, and foot temperatures were higher at the room temperature of 27° C. than they were at 25° C. (Tables I and II). Analysis of Tables I and II shows that the average rectal temperature of the subjects who were studied at 27° C. was only 0.15° C. higher than that of those who were studied at 25° C. On the other hand, the average skin temperature was increased 0.74° C. by the higher room temperature. These observations serve to illustrate two points: In the first place, Hardy and DuBois¹⁶ have shown that the average skin temperature increases about 0.5° C. for each 1.0° C. rise in environmental temperature. They made observations on their subjects in the Russell-Sage Calorimeter. Although a calorimeter was not employed by us, our results show close agreement with those of Hardy and DuBois;¹⁶ the average skin temperature of our subjects increased 0.37° C. for each 1.0° C. rise in room temperature (Tables I and II). The slight difference in average rectal temperature at the two room temperatures brings out the second point. Although there was a difference in environmental temperature of 2.0° C. between the two groups, the adjustments of human heat regulation were such that the average for the internal temperature of both groups of subjects was approximately the same. The constancy of internal temperature may have been brought about by loss of heat through increased allotment of

blood to the surface, for the average peripheral blood flow was 21 e.e./M²/Min. higher at the higher room temperature (Tables I and II).

In those subjects upon whom more than one observation was made, the average internal and surface temperatures varied from one day to the next. In addition, these data and those of single observations show that the highest skin temperature did not always occur with the higher rectal temperature, and the warmest hands and feet were not always associated with the warmest skin (Tables I and II). It becomes apparent, therefore, that no direct relationship existed between any of the individual local temperatures.

The blood pressures and pulse rates of all the subjects were normal. Small variations which occurred from day to day in the same subject were of no significance.

SUMMARY

By means of a method which has been employed by us in other studies,¹⁻⁷ seventy-five measurements of the peripheral blood flow in e.e./M²/Min. were made on thirty-four normal male subjects. In addition, the basal metabolic rates, blood pressures, and pulse rates were recorded. The results may be summarized as follows:

1. The peripheral blood flow under basal conditions at 25° C. room temperature showed a range from 8 to 78 e.e./M²/Min. in all instances except one, in which it was consistently higher. Peripheral blood flow was usually less with a lower basal metabolic rate and greater with a higher basal metabolic rate. The average for all subjects at this temperature was 52 e.e./M²/Min.

The peripheral blood flow of the subjects who were studied at 27° C. room temperature ranged from 34 to 157 e.e./M²/Min. except for two instances, in which it was 8 and 13 e.e./M²/Min., respectively. Again, the peripheral blood flow usually varied in the same direction as the basal metabolic rate. The average for all subjects at this temperature was 73 e.e./M²/Min.

There was overlapping of the level of peripheral blood flow at the two room temperatures, but, on the average, the flow was greater at the higher temperature. In four subjects who were studied at both room temperatures, the peripheral blood flow was greater at the higher room temperature.

2. The average basal metabolic rate was the same in the two groups; that is to say, it was minus 6 per cent at 25° C., and minus 5 per cent at 27° C. Small increases in basal metabolism were recorded in 60 per cent of the experiments at the end of a morning's observations, and small decreases in 40 per cent. These changes were not of sufficient magnitude to be considered significant.

3. The average rectal, skin, hand, and foot temperatures were higher at the higher room temperatures (27° C.). The increase in average surface temperature was approximately 0.4° C. for each degree rise in

room temperature. At the same time, the average rise in rectal temperature was small. This constancy in rectal temperature appears to have been brought about by the allocation of more blood to the surface of the body at the higher room temperature.

4. The blood pressure and pulse rate were normal in each instance, and there were essentially no differences in the averages for the subjects who were studied at 25° C. and those at 27° C.

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THE EFFECT OF SMOKING CIGARETTES ON THE PERIPHERAL BLOOD FLOW

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THE effects of the smoking of tobacco on the peripheral vascular system has been the subject of many investigations in recent years. Using the fall in finger temperature as an index of decreased peripheral blood flow, Maddock and Coller¹ have shown in man that the effects of smoking standard cigarettes could be reproduced by the intravenous injection of 1.0 mg. of nicotine. Haag² demonstrated in animals that the vasoconstriction and rises in blood pressure occasioned by the intravenous injection of smoke solutions were proportional to their nicotine content. Wright and Moffat³ observed decreases in the finger-tip and toe-tip temperatures and vasoconstriction of the capillary loops of the nail fold, and concluded that there were no appreciable differences between the effects of standard cigarettes and cigarettes which contained only 40 per cent as much nicotine. In Wright and Moffat's experience,³ as well as in that of Maddock and Coller,¹ smoking cigarettes which contained no nicotine was associated with only negligible changes.

Mulinos and Shulman⁴ employed the capillary microscope, the plethysmograph, and the skin temperature in a correlation of the changes that occurred in the extremities as the result of smoking and deep breathing. They likewise found no difference in the effects of tobacco cigarettes of varying strengths. Moreover, they were of the opinion that the greater part of the observed decrease in peripheral blood flow could be accounted for by deep breathing. Abramson, Zazeela, and Oppenheimer,⁵ who made plethysmographic studies of the hand, forearm, and foot, concluded that smoking probably causes decreased blood flow in the skin and not in the voluntary muscle. There is, therefore, confusion about the effect that tobacco has on the peripheral blood flow.

Observations on the peripheral blood flow in all of these studies,¹⁻⁵ as pointed out, were based upon changes in the volume of an extremity as recorded by modified plethysmographs, on inferences about blood flow from changes in the skin temperature of an extremity, or on direct observation of the capillary loops of the nail fold. Since a relatively new method was available for the measurement of peripheral blood

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flow,⁶ it seemed worth while to reinvestigate the effects of the smoking of tobacco, and make a comparison with cigarettes which contained no nicotine.

In the study now being reported, all of the subjects smoked regular (standard) cigarettes, commercially denicotinized cigarettes, and cigarettes made from cornsilk. Cornsilk was selected as a control substance because it contains no nicotine. Four observations were made on three of the subjects to secure data concerning the effect of fully denicotinized cigarettes.⁶ In addition, two of the subjects smoked cigarettes through a water pipe. Measurements of the peripheral blood flow were made before, during, and after smoking. Ten normal male subjects whose ages ranged from 19 to 36 years were selected for study. Most of the subjects were physicians from the house staff of the New York Hospital.

METHOD

The measurements of peripheral blood flow were made by means of a modification⁶ of the method of Hardy and Soderstrom.⁷ Hardy and Soderstrom have shown that, at temperatures below 28° C., the skin functions like a dead insulator when the subject is lying nude in the basal state, and that blood flow to the skin, thermal conductivity of the peripheral tissues, and vaporization are constant and minimum. With an increase in blood flow to the periphery, more heat is brought from the deeper tissues to the surface; this increases the thermal conductance of the superficial tissues, and, therefore, changes in thermal conductance become an index to peripheral blood flow. With this method, blood flow is expressed as a function of heat loss, surface area, *average skin temperature*, and rectal temperature. The method requires the recording of skin and rectal temperatures at known intervals, and of oxygen consumption, height, and body weight. The skin temperatures were recorded with a Hardy-Soderstrom radiometer from 11 points on the anterior surface of the body. With this method the amount of blood allocated to the whole periphery of the body is measured, rather than the flow in local areas, and may be expressed as e.c./M²/Min. In addition, the blood pressures and pulse rates were recorded between temperature readings. Electrocardiograms, including Lead IV F, were taken immediately before and during the smoking of the various types of cigarettes.

PLAN OF PROCEDURE

The plan of procedure was essentially the same as that described in a recent publication.⁶ In the present study, measurements of skin and rectal temperatures were made at ten-minute intervals instead of at twenty-minute intervals, as in previous work. Each set of measurements covered ninety minutes. The blood pressures and pulse rates were recorded during free intervals between temperature readings. The basal metabolic rate was measured before smoking, immediately after smoking, and again at the end of a morning's observations. For the period before smoking the first basal metabolic rate was used in the calculation of peripheral blood flow. For the period during smoking the average of the oxygen consumption before and immediately after smoking was used for calculating peripheral blood flow. For the phase after smoking, the difference between the oxygen consumption immediately after smoking and that at the conclusion of the experiment was divided by the

*We wish to thank Dr. Harvey B. Haag, Professor of Pharmacology, Medical College of Virginia, Richmond, Va., for generously furnishing the authors with fully denicotinized cigarettes.

number of periods of peripheral blood flow measurements in such a way that it was properly apportioned among these periods. One type of cigarette was smoked during a morning's observations. Only those subjects were chosen who were accustomed to smoke and inhaled while smoking. The subjects smoked, in succession, two-thirds of two cigarettes at their normal inhalation depth and frequency; exaggerated smoking was avoided. The duration of smoking varied with the subjects from sixteen to eighteen minutes. A room temperature of 27° C., with a relative humidity of approximately 40 per cent, was maintained. The cigarettes, whether regular (standard) or commercially denicotinized, were of the

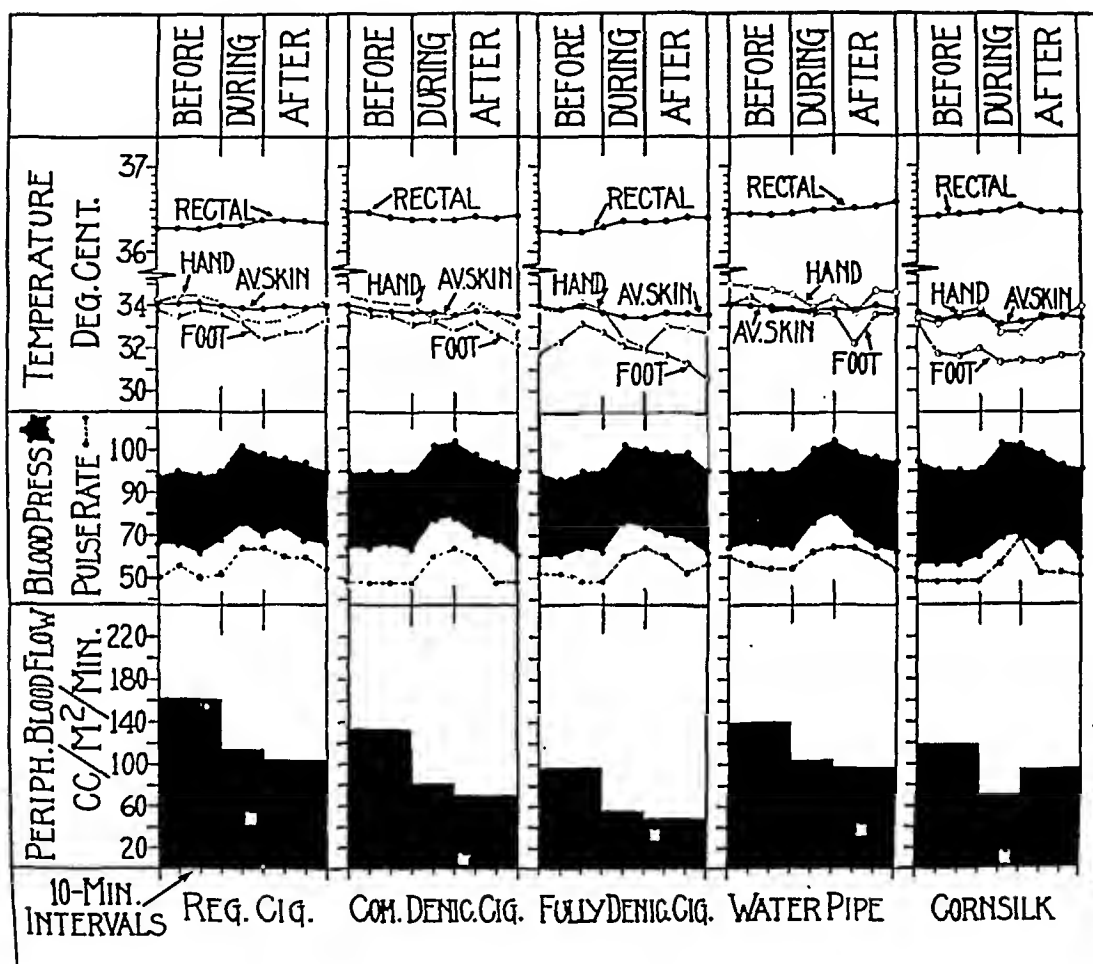


Fig. 1.—Data relating to the effect of smoking different types of cigarettes on Subject G. V. The open square in the solid areas indicating the average peripheral blood flow marks the lowest level the peripheral blood flow reached as a consequence of smoking.

same brand for all subjects. They were purchased on the open market. The regular and commercially denicotinized cigarettes contained 1.88 per cent and 0.79 per cent of nicotine, respectively.⁸ When the water pipe was employed, commercially denicotinized cigarettes were used. The fully denicotinized cigarettes were prepared after the technique of Weatherby.⁹ Cigarettes made from cornsilk were of approximately the same size, weight (1 Gm.), and texture as the foregoing types.

RESULTS

The data relating to subject G. V. (Fig. 1) serve to illustrate the effects of smoking the different types of cigarettes. The averages for

all subjects are shown in Fig. 2. The data on all subjects are summarized in Table I.

Effect of Smoking on Peripheral Blood Flow.—The peripheral blood flow decreased in all instances during smoking, regardless of whether the cigarettes were regular ones, commercially denicotinized, fully denicotinized, or made of cornsilk (Fig. 1, Table I). In all instances the

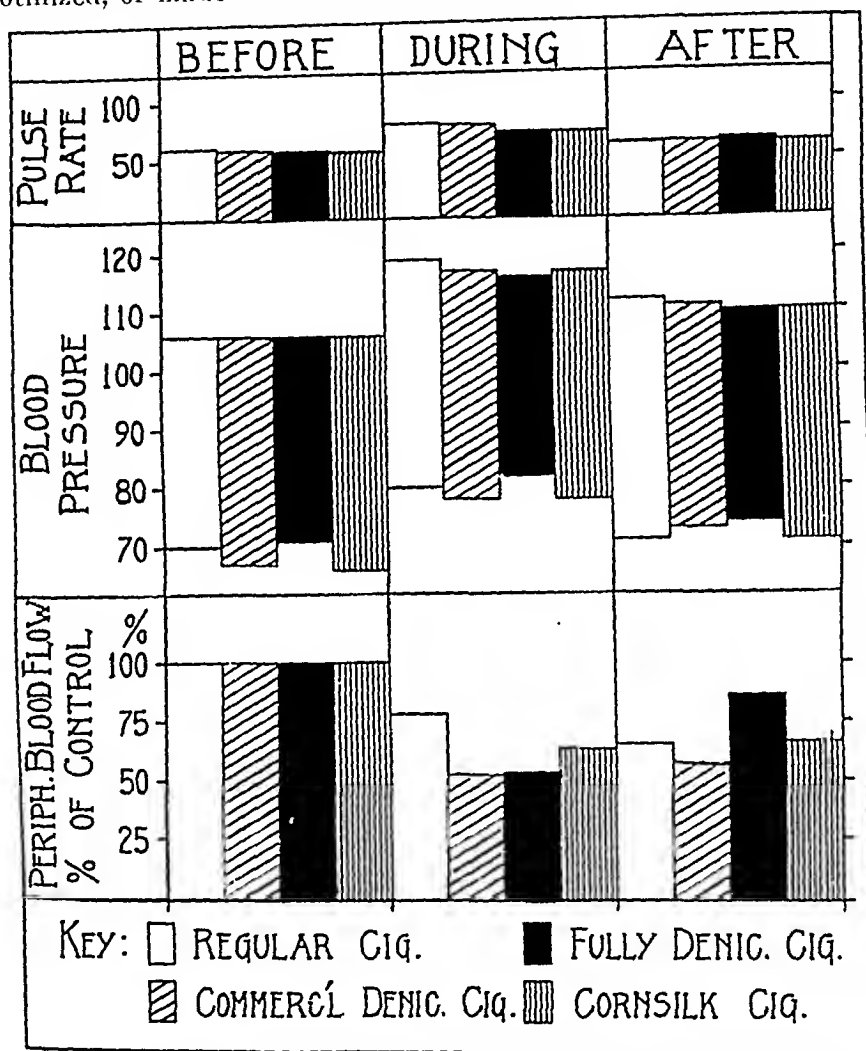


Fig. 2.—Changes in average peripheral blood flow as per cent of the control levels, as well as the average blood pressures and average pulse rates of all subjects before, during, and after smoking regular, commercially denicotinized, and fully denicotinized cigarettes, and cigarettes made from cornsilk.

peripheral blood flow continued to fall in one or more experiments in the first part of the period after the subjects had stopped smoking, but began to rise toward the control levels by the end of thirty minutes after cessation of smoking. In others, after the fall in peripheral blood flow which accompanied smoking, there was a return to control levels as soon as the smoking was discontinued. In the average values given for the periods before, during, and after smoking these trends would not be shown (Table I).

TABLE
DATA RELATING TO THE EFFECT

SUB- JECT SEX AGE	CIGARETTE TYPE*	AV. PERIPHERAL BLOOD FLOW C.C./M ² /MIN.				AV. BLOOD PRESS. MM.Hg			AV. PULSE RATE PER MIN.		
		BE- FORE	DUR- ING	AFTER	LOWEST LEVEL AS RESULT OF SMOK- ING†	BEFORE	DURING	AFTER	BE- FORE	DUR- ING	AFTER
G. V. Male 19	Reg. cig.	163	115	105	54	99/65	111/74	103/69	52	62	58
	Comm. denic.	134	82	71	2	100/65	112/77	104/66	48	61	48
	Fully denic.	97	56	54	38	99/62	111/74	106/67	49	61	55
	Water pipe	140	104	97	42	100/65	112/78	107/66	55	63	59
	Cornsilk	119	71	95	0	101/57	112/69	103/63	48	62	52
E. B. Male 24	Reg. cig.	119	68	76	0	102/72	117/83	107/73	67	83	71
	Comm. denic.	85	50	40	25	107/73	119/81	119/90	61	83	73
	Fully denic.	49	35	67	0	107/80	117/86	108/78	67	80	69
	Water pipe	97	50	48	0	106/70	122/86	118/78	62	70	67
	Cornsilk	70	24	32	12	100/68	118/86	109/79	68	79	65
F. H. Male 28	Reg. cig.	46	19	37	14	94/62	108/76	111/70	59	67	61
	Comm. denic.	113	58	129	58	101/68	108/71	105/67	64	70	60
	Fully denic.	41	8	38	0	113/71	123/86	117/77	59	80	67
	Fully denic.	67	36	63	36	101/69	114/80	107/73	56	72	72
	Cornsilk	72	34	32	0	106/61	118/81	107/71	61	76	61
R. T. Male 28	Reg. cig.	60	39	65	39	114/73	126/86	120/79	65	96	72
	Comm. denic.	108	44	23	14	108/69	124/84	115/77	59	91	68
	Cornsilk	86	46	41	9	111/70	119/83	117/76	60	88	63
F. D. Male 22	Reg. cig.	61	56	101	56	103/70	118/80	109/71	57	69	57
	Comm. denic.	126	73	50	10	103/70	118/80	109/71	58	72	62
	Cornsilk	116	2	53	2	107/73	118/83	109/73	60	78	62
W. B. Male 30	Reg. cig.	77	44	25	0	112/67	119/83	120/79	56	79	65
	Comm. denic.	54	4	101	4	103/67	121/85	109/76	61	92	76
	Cornsilk	72	34	32	0	95/69	114/76	114/66	42	76	66
L. E. Male 31	Reg. cig.	87	95	24	0	105/69	123/74	112/60	55	88	63
	Comm. denic.	72	68	14	0	112/61	120/72	117/65	43	91	62
	Cornsilk	49	95	23	3	105/60	119/67	110/65	50	65	49
M. McC. Male 36	Reg. cig.	13	21	8	0	101/64	114/69	114/67	60	69	60
	Comm. denic.	87	45	99	0	96/58	108/71	102/69	64	73	59
	Cornsilk	83	39	33	0	96/64	106/67	107/67	57	65	65
R. B. Male 27	Reg. cig.	39	10	55	10	105/69	122/81	117/77	60	86	76
	Comm. denic.	89	74	43	0	106/70	113/81	109/75	65	78	69
	Cornsilk	35	44	12	0	100/70	117/79	109/75	63	75	70
W. S. Male 28	Reg. cig.	82	85	30	0	121/81	133/94	121/80	71	102	63
	Comm. denic.	93	2	34	0	113/73	124/90	115/79	71	91	83
	Cornsilk	83	70	33	0	112/76	127/90	118/77	55	68	59

*Key: Reg. cig. = regular or standard cigarettes (approx. 1.9 per cent nicotine)

Comm. denic. = commercially denicotinized cigarettes (approx. 0.8 per cent nicotine)

Fully denic. = fully denicotinized cigarettes (contain no nicotine; prepared according to technique to be reported by Weatherby)

Water pipe = comm. denic. cigarettes smoked through a water pipe containing cold water (nicotine and some irritating substances removed)

Cornsilk = cigarettes made from cornsilk (no nicotine)

†Lowest observed level of blood flow as the result of smoking (amounts too small to measure are marked zero—0).

I

OF SMOKING ON 10 SUBJECTS

BASAL METABOLIC RATE PER CENT			MAX. TEMP. INCREASE OR DECREASE AS RESULT OF SMOKING ° C.							
BEFORE	DURING	AFTER	RECTAL		AV. SKIN		HAND		FOOT	
			IN- CREASE	DE- CREASE	IN- CREASE	DE- CREASE	IN- CREASE	DE- CREASE	IN- CREASE	DE- CREASE
-6	-11	-10	0.05			0.17		1.1		1.2
-14	-14	-12	0.04			0.12		1.0		1.0
-18	-14	-14	0.10			0.21		1.3		2.1
-4	0	+3	0.13			0.06		0.8		1.6
-11	-9	-6	0.08			0.44		1.1		0.6
+2	+5	+7	0.10		0.55			0.4		0.6
0	-2	+4	0.07			0.03		0.4		1.1
-10	-9	-8	0.05		0.25			0.5		0.4
+12	+8	+10	0.18		0.17			1.1		3.0
-4	-7	-7	0.17			0.10		0.1		1.5
-2	0	+4	0.17			0.42		0.6		0.9
+2	+4	+6	0.16			0.67		0.5		0.6
-5	-13	-6	0.08			0.03	0.2			0.7
-4	0	+7	0.15		0.24		0.2			0.6
+5	+2	+2	0.17			0.13		0.2		1.1
-19	-15	-13	0.02			0.08		0.8		3.2
-10	-9	-13	0.07			0.17		1.1		3.8
-18	-16	-14	0.06			0.16		1.2		2.8
-13	-6	0	0.05			1.10		1.3		2.9
-6	-5	-5	0.26			0.35		0.5		2.6
-5	+1	+3	0.13			0.53		1.2		2.5
-3	-6	-7	0.20			0.52		0.5		1.0
+1	+3	+5	0.11			0.31		0.4		0.7
+1	-2	0	0.09			0.12		0.2		1.0
-10	-3	+2		0.08		0.67		0.8		1.6
-13	-4	0	0.29		0.26			1.3		1.4
-10	-9	-5	0.12			0.37		1.1		2.3
-23	-18	-15	0.04			0.22		0.2		1.6
-19	-18	-15	0.06			0.26		1.0		1.5
-19	-16	-11	0.20			0.31		0.6		1.1
+1	0	0	0.05			0.40		0.1		0.2
+3	-3	-7	0.05			0.34		1.4		1.9
-10	+1	-10	0.15			0.23		0.9		1.2
0	-6	-11	0.05			0.46		0.2		2.1
-10	-7	-8	0.13			0.07		1.3		2.6
-12	-11	-15	0.17			0.41		1.2		1.6

Effects of Smoking on Basal Metabolism.—The basal metabolic rate increased slightly, either immediately after smoking or at the conclusion of the measurements, about twice as often as it decreased, regardless of the type of cigarette smoked (Table I). The increases or decreases in oxygen consumption, however, were no greater and were of the same frequency as those among persons of the same age group who lay quietly for the same length of time without smoking.¹⁰

Effect of Smoking on Blood Pressure and Pulse Rate.—Both the blood pressure and pulse rate rose after smoking every type of cigarette. The rises were of approximately the same magnitude and duration, regardless of the type of cigarette. Similar changes took place when the water pipe was used (Fig. 1, Table I).

Effect of Smoking on Skin Temperature.—A decrease in average skin and hand temperature occurred during and after the smoking of each type of cigarette in all but five instances (Subjects E. B., L. E., and F. H., Table I), and two instances (Subject F. H., Table I), respectively. The foot temperature always decreased. The decrease in the temperature of the hand and foot as the result of smoking was greater than average variations in skin temperature. By comparison, the fall in foot temperature was more marked in most instances than that in hand temperature (Table I, Fig. 1).

Effect of Smoking on Rectal Temperature.—The rectal temperature rose after smoking in all except one instance (Subject L. E.), and to approximately the same extent regardless of the type of cigarette (Fig. 1, Table I).

Effect of Smoking on Electrocardiograms.—Smoking every type of cigarette resulted in an increase in heart rate. The most common change was a decrease in the amplitude of the T waves in one or more leads; this occurred in 71 per cent of the tests. An increase in amplitude occurred in 20 per cent of the tests, and no change in 9 per cent. When the amplitude decreased in several leads it might increase in one lead, or the T wave might become negative, decrease in negativity, or become upright. No correlation was apparent between an increase or decrease in amplitude and the type of cigarette. That is to say, as marked a change was produced by smoking cornsilk, fully denicotinized cigarettes, or commercially denicotinized cigarettes as by smoking regular cigarettes. The maximum change in amplitude was about 1 mm. The greatest change usually accompanied the greatest change in heart rate.

DISCUSSION

The peripheral blood flow decreased as the result of smoking in all instances, regardless of whether the subjects smoked regular, commercially denicotinized, fully denicotinized, or cornsilk cigarettes, or smoked cigarettes through a water pipe (Table I, Fig. 2). It must be emphasized that the subjects were normal persons in the third decade of life,

and were free from arterial disease. The greatest percentage decrease in blood flow took place when the subjects smoked commercially and fully denicotinized cigarettes (Fig. 2). In some instances the peripheral blood flow continued to fall after the subject stopped smoking, but in all it had begun to return to, or had attained, control levels at the end of thirty minutes after smoking (Table I, Fig. 1). The kind of cigarette smoked had no bearing on whether the peripheral blood flow continued to fall or began to return toward control levels, or on how much the peripheral blood flow decreased as the result of smoking (Table I).

Wright and Moffat³ observed a decrease in the blood flow in the finger tip and toe tip when their subjects smoked cigarettes containing nicotine, but no effect when cigarettes prepared from shredded, ashless filter paper were smoked. We used cornsilk as a control because cigarettes made from it simulated tobacco cigarettes in texture, weight (approximately 1 Gm.), size, and moisture content, and the smoke could be inhaled with ease. Ease of inhalation of the smoke and the basal metabolic state were required in order to have as many factors constant as possible. Ashless filter paper cigarettes prepared according to the technique of Wright and Moffat³ did not conform to the standards as set forth in the plan of procedure. We prepared and attempted to use a cigarette made of ashless filter paper in order to repeat Wright and Moffat's observations with our method of measuring peripheral blood flow. Because the smoke could not be inhaled without causing violent coughing, data collected on two subjects (L. E. and W. S., Table I) with the use of these cigarettes were not considered sufficiently accurate for comparison, and further tests were not carried out.

Our observations on peripheral blood flow with respect to the smoking of regular cigarettes were similar to the inferences drawn by Maddock and Collier¹ and Wright and Moffat³ from the fall in skin temperature. On the other hand, when their subjects smoked cigarettes that contained no nicotine, only a negligible fall in the skin temperature of the fingers was observed. Using euhb for comparative or control cigarettes, as was done by Maddock and Collier,¹ may lead to confusion, for this substance may have some medicinal properties, and is employed in the treatment of asthma.

Our observations are not strictly comparable to those of Maddock and Collier¹ and Wright and Moffat³ because they measured the temperature of the fingers, which is labile. In the method we employed the average skin temperature is secured by weighting temperatures from several parts of the body.⁶ The temperature and blood flow in one part of the body may alter in a different way from another part of the body.

The method we employed in these studies takes account of the peripheral blood flow for the whole body surface in c.c./M²/Min. The surface area of the hands and feet together represents 12 per cent of the total body surface, according to the estimates of Hardy, DuBois,

and Soderstrom;¹¹ the finger¹ and the finger tips and toe tips³ constitute only a very small percentage of these parts. Moreover, the method we have employed not only takes into account the other 88 per cent of the surface area, but also the rectal temperature, which has been given a weighting of 80 per cent of the total body mass by Hardy, DuBois, and Soderstrom.¹¹

Mulinos and Shulman⁴ have stated that deep breathing alone can account for the greater part of the decrease in blood flow to the hand. In thirteen of sixteen subjects they found that a single deep breath caused complete cessation of blood flow through the capillary tuft of the nail fold. Deep breathing of room air did not bring about this result in any of the subjects studied by Wright.¹² Mulinos and Shulman⁴ and Wright,¹² however, did not qualify the depth of the inspiration taken by their subjects. If their subjects took a full inspiration, their inhalations would be exaggerated in comparison with those during *normal* smoking. In the studies now being reported, exaggerated smoking technique was *not* employed. The subjects inhaled, as mentioned earlier, with their normal depth and frequency. This type of inspiration did not induce any significant change in skin temperature. Moyer and Maddock¹³ found that when smoking was simulated, only negligible effects were observed in their subjects. We measured the effect of breathing pure oxygen and hot air upon the peripheral blood flow, and observed no decrease in blood flow or rise in blood pressure or pulse rate. Decreases in blood flow as the result of smoking the various types of cigarettes used in this study, therefore, were not attributed to the nicotine content, to the depth of inspiration, or to the inhalation of oxygen or hot air, but to the smoke itself.

As a result of smoking the different types of cigarettes, the basal metabolic rate of the group increased slightly about twice (69 per cent) as often as it decreased (31 per cent) (Table I). Eighty-two per cent of the subjects studied by Hiestand, Ramsey, and Hale¹⁴ showed an increase in basal metabolic rate. Their subjects smoked regular cigarettes only, and were not studied under basal conditions. The results of our studies on subjects in the basal metabolic state showed that, when regular cigarettes were smoked, slight increases occurred in 69 per cent, and decreases in 31 per cent, of the observations (Table I). These data are in close agreement with recent measurements by Goddard and Voss.¹⁵ Their subjects were observed while smoking regular cigarettes under basal conditions. They found an increased metabolic rate in 60 per cent of their subjects and a decreased rate in 35 per cent. These changes do not appear to be significant with respect to the effect of tobacco on the basal metabolic rate, for the increases and decreases in oxygen consumption were no greater than those which occurred in normal persons of the same age, who lay quietly for the same length of time without smoking.¹⁰

Increases in pulse rate and blood pressure were observed as the result of smoking the various types of cigarettes. These changes were of the same magnitude and duration, regardless of the kind of cigarette (Figs. 1, 2) (Table I). Main¹⁶ found that fully denicotinized cigarettes caused less rise in blood pressure and pulse rate than did regular cigarettes. His results, however, were obtained from a standard exaggerated smoking technique. Maddock and Coller¹ observed no change in blood pressure or pulse rate when their subjects used a water pipe or smoked enbeh, but definite increases in blood pressure and pulse rate occurred when regular cigarettes were smoked. When our subjects used the water pipe, a definite increase in blood pressure and pulse rate was observed (Table I, Fig. 1). The difference between these observations and those of Maddock and Coller¹ may possibly be explained by the choice of method. The use of enbeh, as mentioned earlier, as a control makes evaluation of the results difficult, because it has been smoked by asthmatics to relieve their attacks. If smoke itself brings about peripheral vasoconstriction, with increases in blood pressure and pulse rate, it seems quite possible that these effects may have been nullified by that substance in enbeh which relieves attacks of asthma. Although the subjects of Wright and Moffat³ smoked cigarettes which contained no nicotine, their report showed no data relating to changes in pulse rate or blood pressure.

There was a decrease in average skin temperature in all except one instance when the subjects smoked regular cigarettes (E. B.), and commercially denicotinized cigarettes (L. E.), but in every instance after cornsilk cigarettes (Table I). Small increases in average skin temperature were observed in two out of four observations, when two of three subjects smoked fully denicotinized cigarettes. Two of the four experiments were done on the same person (F. H., Table I). The first observations on this subject showed a fall in average skin temperature as the result of smoking, the subsequent one, a rise. At the same time, this subject showed small increases in hand temperature and moderate decreases in foot temperature during both experiments. The other subject, who showed an increase in average skin temperature as the result of smoking fully denicotinized cigarettes, also showed an increase when the water pipe was employed. The hand and foot temperatures fell during both experiments on this subject (E. B., Table I).

Not only subjects F. H. and E. B., but each subject in the group showed a varying response to smoking from one experiment to the next. For example, at a time when subject R. B. (Table I) showed the greatest decrease in *average* skin temperature, the least decrease occurred in the temperature of his extremities. Subsequent observations on this subject showed the reverse type of response. Analysis of the data in Table I shows that other subjects responded in a similar manner. These data demonstrate, therefore, that a subject reacted differ-

ently from day to day, and that there was no direct relationship between the average skin temperature and the temperature of the hand or foot (Table I).

Goddard and Voss¹⁵ reported that the body temperature was usually higher after smoking. They did not specify, however, how or where the body temperature was measured. In our experiments, rapid increases in rectal temperature resulted from smoking in all but one instance, in which a fall occurred. This took place when one of the subjects (L. E.) smoked regular cigarettes (Table I). We wish to emphasize the increase in rectal temperature. We think that the sudden rises in rectal temperature are important as an index of peripheral vasoconstriction and decreased peripheral blood flow, for the internal temperature represents about 80 per cent of the total body mass.¹¹ The sudden increases in rectal temperature indicated increased heat storage. Examination of the data showed that increased heat storage could be accounted for only in part by increased heat production (basal metabolism). It follows, therefore, that the body stored heat because peripheral vasoconstriction decreased the allocation of blood to the surface. The peripheral vasoconstriction and decreased peripheral blood flow were such that 80 per cent of the body mass gained heat rapidly.

The most common change in the electrocardiogram caused by smoking was lowering of the amplitude of the T waves. This change was slight, and usually did not exceed 1 mm. An increase in amplitude, as well as no change, was also recorded. Since these effects were produced by smoking cornsilk, fully denicotinized cigarettes, and commercially denicotinized cigarettes, as well as regular cigarettes which contained nicotine, it is apparent that they cannot be attributed to the nicotine content of smoke. These results are similar, in the main, to those described by Graybiel, Starr, and White.¹⁷ They attributed the changes which they recorded to the nicotine content of tobacco smoke, but our observations make it appear unlikely that nicotine is responsible. The changes are similar to those observed by Hartwell, Burrett, Graybiel, and White¹⁸ after exercise and atropinization, and may be associated with the increase in heart rate and whatever adjustments increase in rate may require in the organism.

The observations now being reported have shown that smoke which contained *no* nicotine had the same effect (decrease in peripheral blood flow, increase in blood pressure and pulse rate) as smoke which contained it. It is apparent that nicotine cannot be responsible for the effects we have observed, and the question naturally arises as to what the cause may be. Willius, in the course of his discussion of a paper on "Tobacco and Coronary Disease," by English, Willius, and Berkson,¹⁹ said, in part: "You will note that we have carefully avoided the use of the term *nicotine*, but said *tobacco smoke*, because we have

reasons to believe that probably more than the chemical agent nicotine plays a part."

Haag,² working with animals, demonstrated that the effects of smoke solutions were proportional to their nicotine content. In addition, it has been shown by Maddock and Coller¹ and Haag² that nicotine alone, without smoke, may induce changes in the circulation similar to those we have described. The work of Haag indicates that nicotine has a quantitative effect, but the results of Wright and Moffat³ and Mulinos and Shulman⁴ showed no essential difference between the effects of smoking standard cigarettes and cigarettes which contained only 40 per cent as much nicotine. If nicotine had been the responsible factor in our experiments, changes of greater magnitude might have been expected from cigarettes which contained it because of the additive effect of smoke and nicotine, for denicotinized cigarettes brought about similar changes. Such an additive effect was not observed in any instance. Sympathetic stimulation brought about by the irritating effect of smoke upon the respiratory tract, independent of nicotine, may be responsible for the changes we have observed.

The smoking of tobacco has been generally regarded as deleterious in certain peripheral vascular diseases. The data now being presented indicate that smoking any type of cigarette may be harmful, and that smoking denicotinized cigarettes is not a substitute for not smoking.

SUMMARY

The effect of smoking cigarettes on the peripheral blood flow was studied by means of a method with which the average amount of blood allotted to the periphery can be measured in c.c./M²/Min. Peripheral blood flow was measured in ten normal male subjects. Effects on the electrocardiogram, basal metabolic rate, blood pressure, and pulse rate were also recorded. Studies were made before, during, and after the smoking of regular cigarettes, commercially denicotinized cigarettes, and cigarettes made from cornsilk. Observations were made on ten male subjects whose ages ranged from 19 to 36 years. Four observations relating to fully denicotinized cigarettes were made on three of the subjects. Measurements were made also when two of the subjects smoked cigarettes through a water pipe.

1. As a result of smoking, a decrease in peripheral blood flow occurred in every instance, regardless of the type of cigarette smoked. After cessation of smoking, the peripheral blood flow continued to decrease in some cases and began to return toward control levels in others. In all, a return toward normal had begun by the end of thirty minutes after smoking had stopped.

2. An increase in blood pressure and pulse rate of essentially the same magnitude and duration resulted from smoking every type of cigarette.

3. The average skin temperature decreased in all but five experiments. The hand temperature fell in every instance except two. The foot temperature always decreased. The decrease in foot temperature was greater than that in hand temperature on all but two occasions.

4. Rapid rises in rectal temperature occurred in all experiments except one. These rapid rises in rectal temperature were considered an important index to peripheral blood flow.

5. As the result of smoking, small increases in basal metabolic rate were observed about twice as often as small decreases. The change had no relationship to the kind of cigarette, and was of about the same amount and duration as the changes which occur when normal subjects lie in bed for the same length of time without smoking.

6. The changes in the electrocardiogram were slight and probably of no significance.

7. Since these changes occur after smoking cigarettes which do not contain nicotine as well as those which do, they are not to be attributed to nicotine. It is suggested that sympathetic stimulation brought about by the irritating effect of smoke upon the respiratory tract may be responsible for the changes we have observed.

8. It appears that smoking not only regular cigarettes, but also denicotinized cigarettes or cigarettes of any type should be avoided in the presence of peripheral vascular disease.

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THE COURSE OF THE BLOOD PRESSURE BEFORE, DURING, AND AFTER CORONARY OCCLUSION

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AN EARLY fall in blood pressure is one of the cardinal signs of coronary occlusion,¹ and its importance in the differentiation of this disease from angina pectoris was recognized as early as 1915.² There has been relatively little systematic study of the course of the blood pressure during the entire attack. Observations on the blood pressure in the years subsequent to the attack have been reported by Palmer³ and Master, et al.^{4, 5} The present report is based on a detailed study of the blood pressure before, during, and after coronary occlusion in a large series of cases.

Particular interest was paid to the following: the influence of hypertension on prognosis during and after the attack; the number of patients who lose their hypertension during the attack and recover it later; the relation of the fall in blood pressure to the height of the blood pressure prior to the attack; the significance of the rapidity and degree of fall in blood pressure and in pulse pressure; the causes of the immediate fall in blood pressure and of the permanent lowering after recovery; the influence of hypertension after the attack on the development of angina pectoris, heart failure, coronary occlusion, and death.

MATERIAL

Blood pressures were recorded frequently after five hundred thirty-eight attacks of acute coronary occlusion. Slightly over half of these were initial attacks and the remainder were second or third attacks (Table I). Four hundred sixteen of the attacks occurred in men and one hundred twenty-two in women (Table II), a ratio of 3.4 to 1, which is usual. Recovery occurred in three hundred eighty-three cases (71 per cent), and two hundred five of these patients were followed for a period of one to seven years (average, three and one-half to four years^{4, 5}). In these cases blood pressure readings were taken every three to six months and were correlated with the degree of functional recovery and the presence of angina pectoris, heart failure, and subsequent attacks of occlusion. The latter occurred in fifty-one patients.

RESULTS

Incidence of Hypertension Prior to the Attack.—We employed the following criteria in judging whether hypertension had been present before the attack: (1) a systolic pressure of 150 mm. or more at any time during observation; (2) a diastolic pressure of 96 mm. or more.

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prior to the attack; (3) a diastolic pressure of 90 mm. or more during or after the attack; and (4) marked enlargement of the heart without obvious cause. The application of these criteria showed that 69 per cent of the patients had hypertension before the attack (Table I). Eleven per cent had been nonhypertensive and the remaining 20 per cent probably had had normal blood pressure, that is, they were seen only after the onset of the attack, and the blood pressure did not reach a hypertensive level even after recovery. The actual incidence of hypertension was doubtless greater than 69 per cent, for, in many cases, this figure was based on readings obtained only during the attack, when the blood pressure was low. In favor of this view is the fact that the incidence of hypertension in the cases of fatal coronary occlusion was much lower than in those of nonfatal occlusion (Table I). Since previous hypertension does not significantly affect the mortality rate in the attack,⁶ one may assume that hypertension was as common when the attack was fatal as when it was not. A low figure was observed among the patients who died because their blood pressure did not return to previous levels. It is probable, therefore, that the incidence of hypertension in our series was at least 70 to 75 per cent.

TABLE I
INCIDENCE OF PREVIOUS HYPERTENSION
538 ATTACKS

ATTACK	NO.	HYPERTENSION	PROBABLY NORMAL B.P.	NORMAL B.P.
Initial				
Nonfatal	207	146 (71%)	53 (25%)	8 (4%)
Fatal	70	34 (49%)	14 (20%)	22 (31%)
Multiple				
Nonfatal	176	136 (77%)	21 (12%)	19 (11%)
Fatal	85	54 (64%)	20 (24%)	11 (12%)
Total	538	370 (69%)	108 (20%)	60 (11%)

TABLE II
INCIDENCE OF PREVIOUS HYPERTENSION BY SEX
538 ATTACKS

SEX	NO.	HYPERTENSION	PROBABLY NORMAL B.P.	NORMAL B.P.
Male	416	267 (64%)	89 (21%)	60 (15%)
Female	122	99 (81%)	17 (14%)	6 (5%)

Hypertension was more frequent with multiple than with initial attacks (Table I) and in women than in men (Table II). Sixty-four per cent of the men and 80 per cent of the women had an elevated blood pressure at one time or another.

The frequency of hypertension increased with age. We have previously shown⁶ that the incidence rises from 28 per cent at the age of 25 to 34 years to 80 per cent at 75 years and over. In the present series, twenty-five patients were less than 40 years old, and only nine

of these (36 per cent) had hypertension. Thus the incidence was half of that in the aged. This relatively low frequency of hypertension in the young was observed also by Glendy, Levine, and White.⁷

TABLE III
COURSE OF BLOOD PRESSURE DURING ACUTE ATTACK
205 CASES

	RAPID FALL	GRADUAL FALL
Hypertensive	34.5%	29.5%
Nonhypertensive	22.5%	13.0%
Total	57.0%	42.5%

The Blood Pressure During the Attack.—The blood pressure always fell during the attack. Although the rapidity and degree of fall varied considerably, we have been able to classify the blood pressure course during and after the attack into several types, according to the initial level, the degree and rapidity of fall and return toward the previous level, and the outcome of the attack. Graphs were drawn to illustrate each type; each graph was based on the actual readings in a representative case. The results are summarized in Table III.

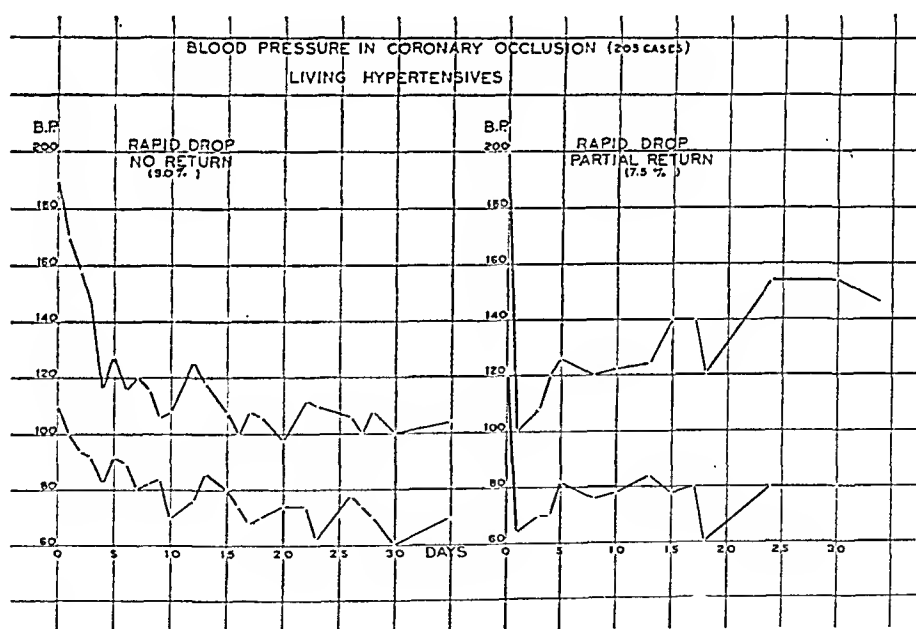


Fig. 1.

Fifty-seven per cent of the patients (Table III) showed a rapid fall, that is, in the first three days the blood pressure fell to a level approaching the lowest pressure during the attack (Figs. 1, 2, 5, 7, 9). In 42.5 per cent the fall was gradual, reaching a low level in one to three weeks (Figs. 4, 6, 8, 9). Occasionally a week or more elapsed before a significant fall became evident; this was observed also by Allen.⁸ In the majority of cases the lowest pressure was reached be-

tween the twelfth and twentieth day (Figs. 2, 3, 4). The rapidity of the fall in blood pressure was influenced to some extent by the height of the pressure preceding the onset of the attack. A greater percentage of nonhypertensive patients showed a rapid fall than did those

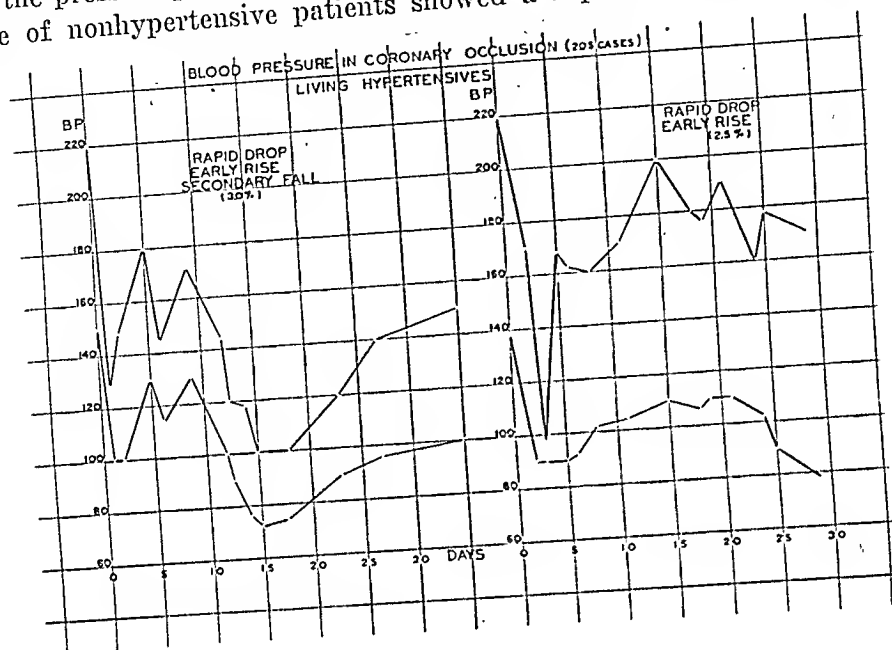


Fig. 2.

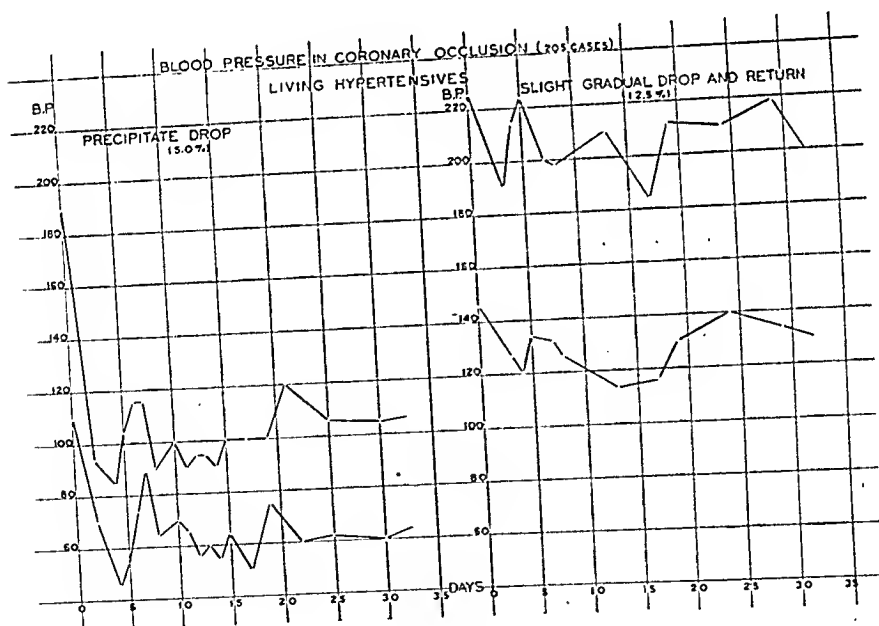


Fig. 3.

with hypertension. The most rapid fall seemed to occur in nonhypertensive cases in which the attack was fatal (Fig. 9). In the hypertensive group the incidence of a rapid fall was the same in the fatal and nonfatal cases. It appears from a study of the graphs that, in general,

TABLE IV

INCIDENCE OF SYSTOLIC BLOOD PRESSURE BELOW 100 MM. DURING ACUTE ATTACK
538 CASES

	HYPERTENSIVE		NONHYPERTENSIVE		TOTAL
	CASES (370)		CASES (168)		538
	NONFATAL	FATAL	NONFATAL	FATAL	
First Day	3%	10%	14%	31%	9%
Lowest	24%	31%	48%	50%	34%
Discharge	4%	21%	19%	28%	13%

the trend of the blood pressure curves was similar in the hypertensive and nonhypertensive groups; of course, the absolute fall in pressure was greater in the hypertensive group.

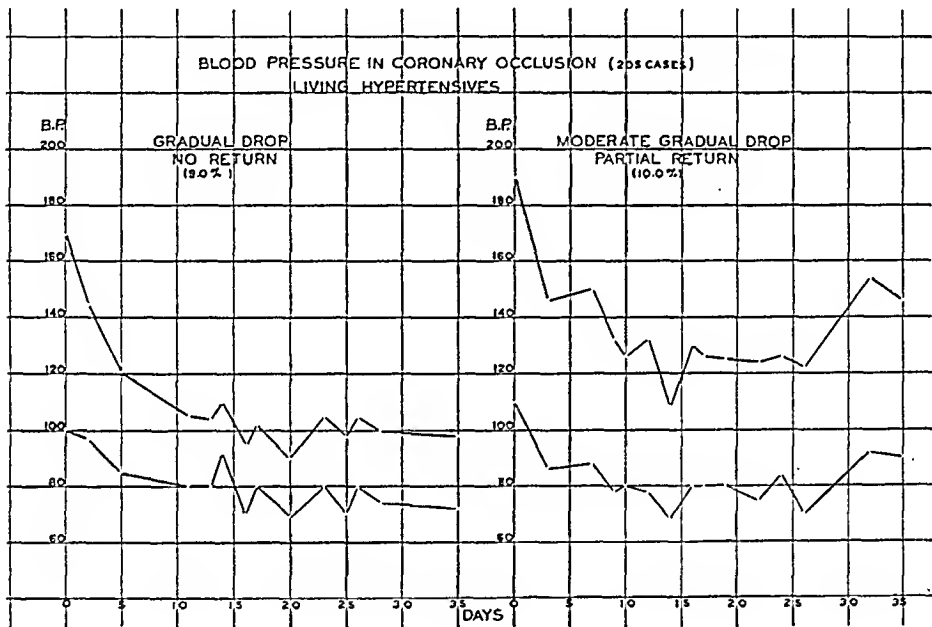


Fig. 4.

Although one is likely to associate coronary occlusion with a precipitate fall in pressure, that is, to less than 100 mm. during the first day, this occurred in only 9 per cent of our cases (Figs. 3, 7, 9). Frequently the fall was not great in the first twenty-four hours (Table IV). In hypertensive patients the systolic pressure rarely fell below 90 mm., and, in only 26 per cent, did it go below 100 mm. during the attack; these figures were practically never reached on the first day of the attack (Table IV). Of the nonhypertensive patients, on the other hand, the systolic blood pressure fell below 90 mm. at some time during the attack in 38 per cent, and below 100 mm. in almost half; the latter level was present on the first day in 22 per cent (Tables IV and VI). As might be expected, the frequency of systolic blood pressures below 100 mm. was greater when the attack was fatal; this was true in both the nonhypertensive and hypertensive groups (Table IV).

The more precipitate and marked the fall, the more severe the attack and the greater the degree of shock.⁸ A systolic pressure below 80 mm. was usually of grave significance.^{1, 9} However, the fall in blood pressure at the onset of the attack was not always of paramount prognostic

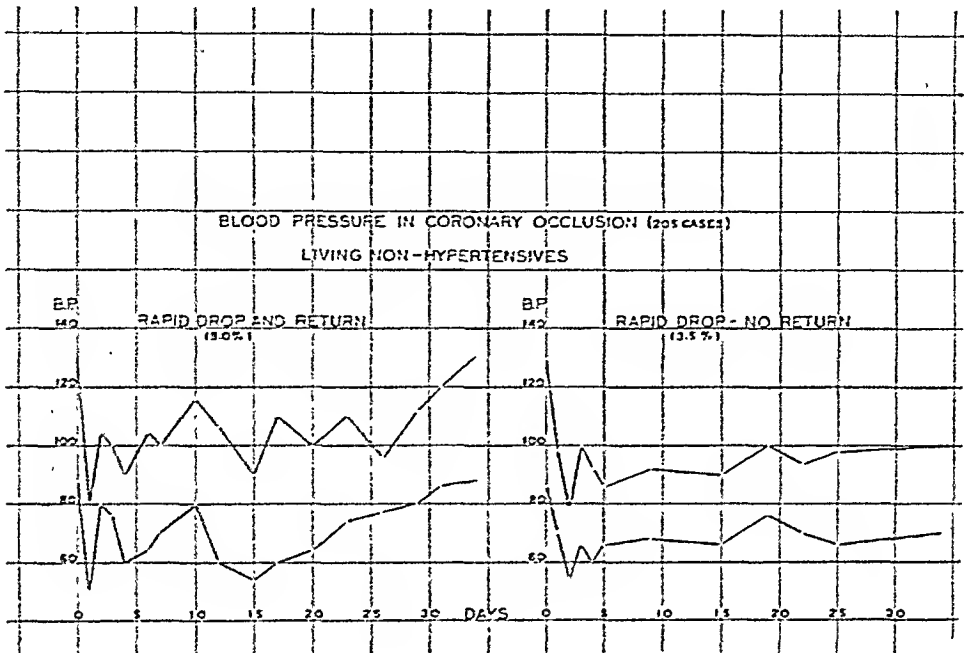


Fig. 5.

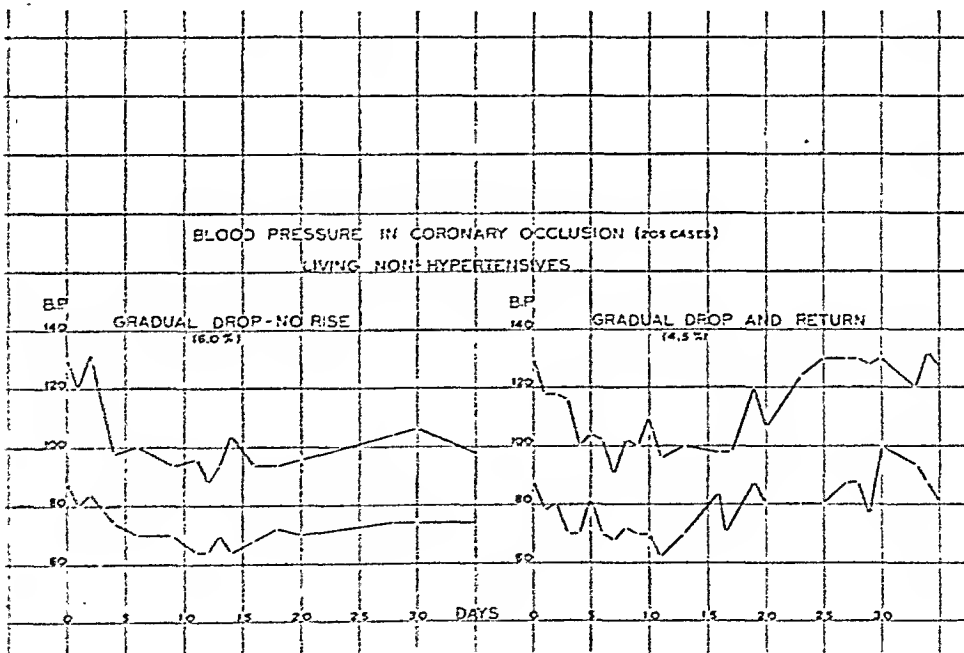


Fig. 6.

significance, for, occasionally, a patient recovered in spite of an initial systolic blood pressure of 70 or 80 mm.¹⁰ On the other hand, two patients died early in the attack when their systolic blood pressure was still over 200 mm.

The actual fall in pressure depended largely upon the initial level (Tables V and VI). Thus, in 20 per cent of the patients who survived and had an initial systolic pressure of 200 mm. or more, the pressure did not fall below 150 mm., and in only 11 per cent did it fall below 100 mm. (Figs. 1 and 2). In this group the pressure not infrequently fell only slightly during the first four or five days (Fig. 3). On the other hand, in the group with a previous blood pressure of 150 to 190 mm., a fall below 150 mm. occurred in all but 3 per cent, and below 100 mm. in 30 per cent (Fig. 4).

TABLE V
RELATION OF PREVIOUS SYSTOLIC BLOOD PRESSURE TO LOWEST PRESSURE
DURING ACUTE ATTACK
198 CASES OF HYPERTENSION

PREVIOUS B.P.	NO.	B.P. DURING ATTACK		
		150-	100-150	100
200-	45	9 (20%)	31 (69%)	5 (11%)
170-199	76	5 (7%)	47 (62%)	24 (31%)
150-169	77	3 (4%)	50 (65%)	24 (31%)
Total	198	17 (8%)	128 (65%)	53 (27%)

TABLE VI
RELATION OF PREVIOUS SYSTOLIC BLOOD PRESSURE TO LOWEST PRESSURE
DURING ACUTE ATTACK
86 PATIENTS WITHOUT HYPERTENSION

PREVIOUS B.P.	NO.	B.P. DURING ATTACK			
		110-119	100-109	90-99	90
130-149	17	3	5	6	3
110-129	61	5	11	20	25
100-109	8	0	1	2	5
Total	86	8 (9%)	17 (20%)	28 (33%)	33 (38%)
Nonfatal	38	4	9	17	8 (21%)
Fatal	48	4	8	11	25 (52%)

Occasionally the onset of coronary occlusion with severe pain was associated with a transitory rise in blood pressure which sometimes reached 200 mm., systolic. This was noted also by Weiss¹¹ and Scherf and Boyd.¹²

Although the blood pressure usually fell progressively, and reached its lowest level between the twelfth and twentieth days (Fig. 1), this was not always the case. In a small group of patients with hypertension, totaling 3 per cent of the series (Fig. 2), the fall in blood pressure was interrupted by a transitory rise early in the attack, followed by a secondary fall in the second week. In another small group (2.5 per cent) of hypertensive patients (Fig. 2), the early rise which followed the initial drop was permanent, and the blood pressure remained elevated throughout the patient's hospital stay, although pre-attack levels were not attained. In cases in which the attack was fatal the blood pressure generally persisted at its lowest levels until death.

However, in a small group of hypertensive patients who survived for several days or weeks, the initial rapid fall was followed by a slight rise before death (Fig. 7). Similarly, in a small group of nonhypertensive patients the blood pressure actually returned to normal before death (Fig. 9).

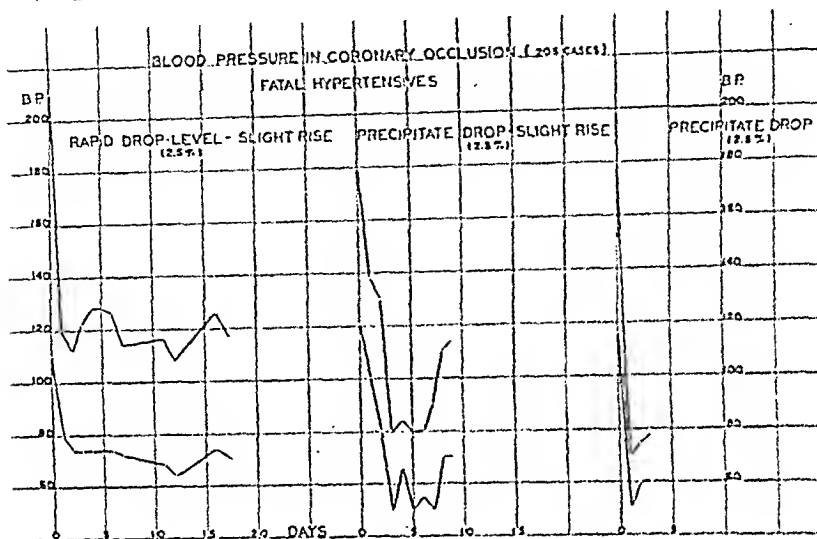


Fig. 7.

TABLE VII

RELATION OF SMALLEST PULSE PRESSURE TO MORTALITY RATE
DURING ACUTE ATTACK

538 CASES

PULSE PRESSURE	HYPERTENSIVES		NONHYPERTENSIVES	
	NO.	MORTALITY	NO.	MORTALITY
70-79	2	0	0	0
50-69	55	21%	2	0
30-49	145	20%	44	18%
20-29	131	23%	69	33%
10-19	36	32%	52	73%
10	1	1 case	1	0
	370	24%	168	40%

The Pulse Pressure During the Attack.—In general, the diastolic pressure followed the same trend as the systolic, but the fall in the former was usually less precipitate and less marked than that in the systolic. This resulted in a decrease in the pulse pressure, often to as low as 10 to 20 mm. (Fig. 2). In the hypertensive group the pulse pressure usually ranged between 20 and 50 mm. (Table VII). In the majority of the nonhypertensive patients it fell between 10 and 40 mm.

In a previous study¹³ it was found that the decrease in pulse pressure was not significant from the point of view of the severity and prognosis of the attack, unless it fell below 20 mm. Coombs¹⁴ regarded a fall to 25 mm. as serious. Our present observations bear out these conclusions. Table VII shows that the mortality rate rose significantly

when the pulse pressure was less than 20 mm. In such cases there is generally a severe degree of shock and heart failure. However, it is interesting that one patient with a pulse pressure of less than 10 mm. recovered.

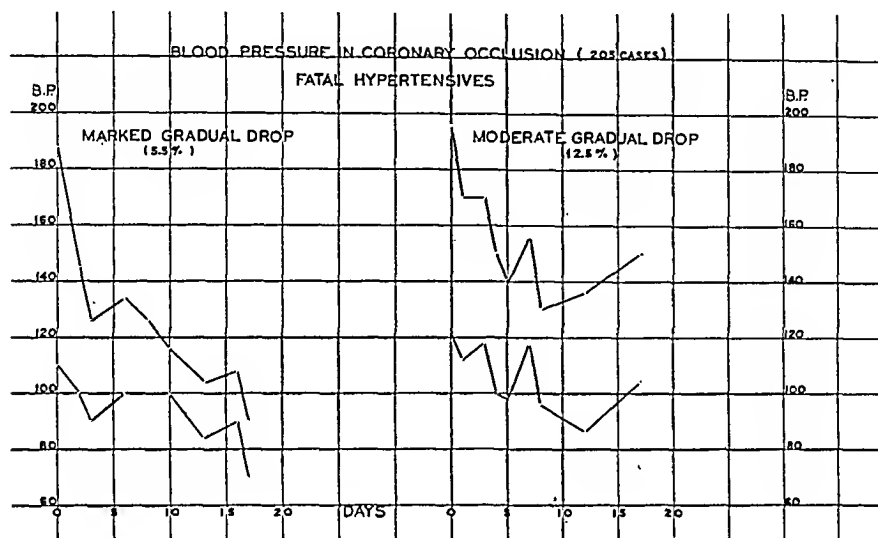


Fig. 8.

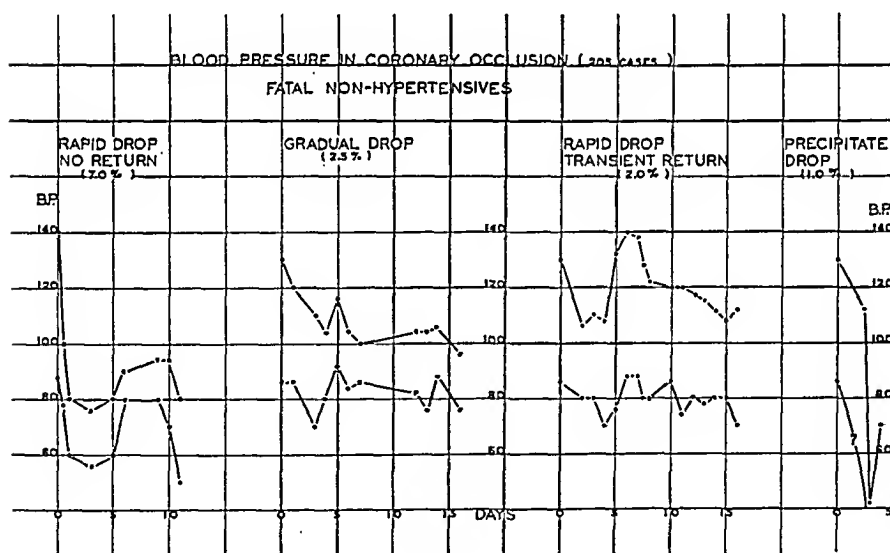


Fig. 9.

Blood Pressure on Discharge.—The blood pressure often persisted at a low level throughout the hospital stay in both hypertensive (Figs. 1, 3, 4) and nonhypertensive patients (Figs. 5, 6); this was true of almost one-third of the patients who survived. In one-third of the entire series there was a gradual return of the blood pressure toward initial levels (Figs. 1, 3, 4, 5, 6). This is shown also by a study of the blood pressures of the patients who survived the attack at the time of their discharge from the hospital (Tables IV, VIII, IX). In the hyper-

tensive group (Table VIII) the blood pressure on discharge had returned to 150 mm. or more in 28 per cent of the cases, and remained below 100 mm. in only 4 per cent (Table IV). The blood pressure generally did not attain the high levels prior to the attack; for example, if the initial pressure had been 170 to 199, the discharge blood pressure was 150 to 169 (Table VIII). It is noteworthy, however, that in two cases the blood pressure on discharge had actually risen to 200 mm. or more.

TABLE VIII
RELATION OF PREVIOUS SYSTOLIC BLOOD PRESSURE TO PRESSURE
AT TIME OF DISCHARGE
160 CASES OF HYPERTENSION

PREVIOUS B.P.	NO.	BLOOD PRESSURE ON DISCHARGE					
		200-	170-199	150-169	120-149	100-119	<100
200+	34	2	8	9	10	6	0
170-199	14	0	1	3	5	4	1
150-169	18	0	0	1	12	5	0
Hypertension of unknown level	94	0	7	14	42	28	2
Total	160	2	16	27	69	43	3
		45 (28%)			115 (72%)		

TABLE IX
RELATION OF PREVIOUS SYSTOLIC BLOOD PRESSURE TO PRESSURE ON DISCHARGE
37 PATIENTS WITHOUT HYPERTENSION

PREVIOUS B.P.	NO.	130-149	BLOOD PRESSURE ON DISCHARGE		
			110-129	100-109	90-99
130-149	8	1	5	2	0
110-129	27	0	13	10	4
100-109	2	0	0	1	1
Total	37	1	18	13	5

As was to be expected, the blood pressure often persisted at lower levels in the nonhypertensive group than in the hypertensive group (Table IX). Thus, in almost one-fifth of the cases the systolic pressure at discharge remained below 100 mm. (Table IV).

Follow-up Study of the Blood Pressure.—In a follow-up study of two hundred twelve cases, Palmer³ observed that more than half of the patients had developed hypertension within one year after the attack. The number with hypertension then increased year by year until the incidence of hypertension reached 72 per cent, which was the same as before the attack. In our series the number of patients who regained their hypertension after the attack was smaller than in Palmer's series.

A study of Figs. 10 and 11, which show the blood pressure readings one month to seven years after the onset of the attack, reveals that the blood pressure failed to return to previous levels in half of the non-hypertensive and one-third of the hypertensive patients. In another third of the hypertensive group the blood pressure rose to a mild

hypertensive level, usually during the first year after the attack. In the remaining third a rapid rise occurred soon after discharge from the hospital, so that, by the end of the year, the blood pressure had attained the high levels which existed prior to the attack. Although

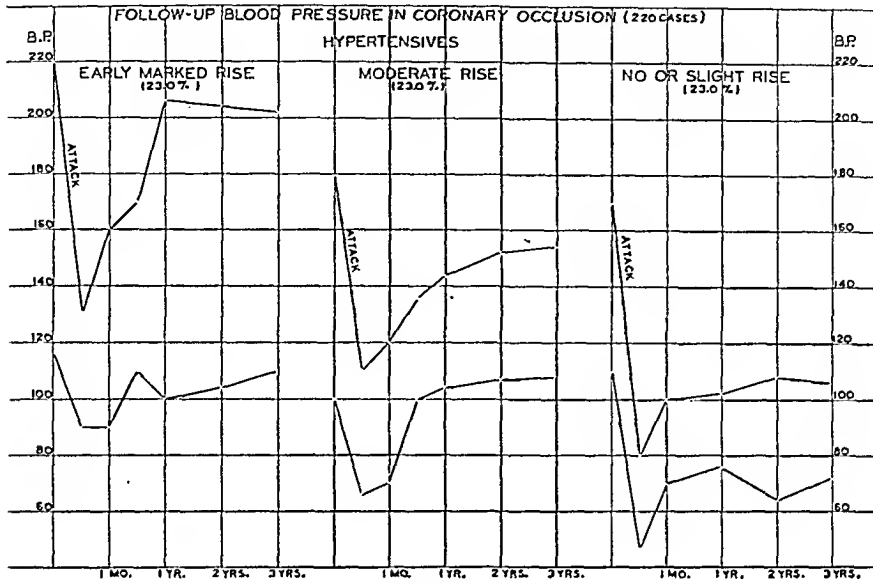


Fig. 10.

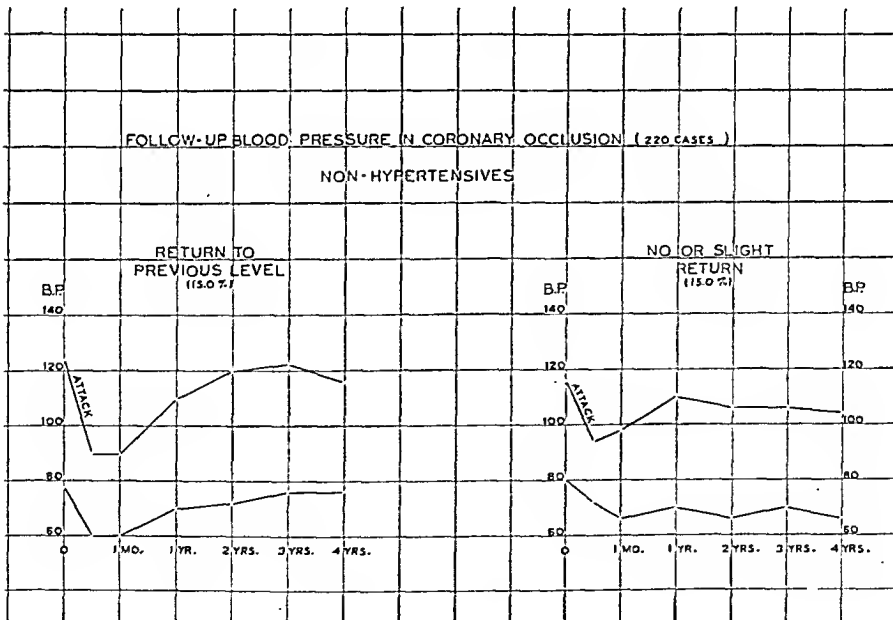


Fig. 11.

this usually occurred within one year after discharge, occasionally the rate of return was slower, so that high levels were reached only in the second or third years. A similar trend was observed in half of the nonhypertensive group.

A summary of these follow-up studies of blood pressure in the hypertensive patients is presented in Table X, in which a comparison is made with previously existing blood pressures. It is seen that the systolic pressure returned to 150 mm. or more in almost two-thirds of the cases. It has already been stated that, in half of these, this level had been reached by the time the patient was discharged from the hospital. In the remaining cases hypertension generally returned during the first or second year. In half the cases in which hypertension returned the blood pressure eventually became approximately the same as before the attack.

TABLE X

RELATION OF PREVIOUS SYSTOLIC BLOOD PRESSURE TO FOLLOW-UP PRESSURE
164 CASES OF HYPERTENSION

PREVIOUS R.P.	NO.	FOLLOW-UP BLOOD PRESSURE				
		200	170-199	150-169	120-149	100-119
200+	8	4	3	0	1	
170-199	14	1	5	4	3	1
150-169	14	0	0	8	5	1
Hypertension of unknown level	128	18	28	32	36	14
	164	23	36	44	45	16
		103 (64%)			61 (36%)	

It is evident from these observations that one-third of our hypertensive patients permanently lost their hypertension after acute coronary occlusion. However, the systolic pressure rarely remained at very low levels, and never below 100 mm.

Relation of Late Blood Pressure Levels to Prognosis.—In the past, conflicting views have been expressed concerning the prognostic importance of the height of the blood pressure after recovery from the acute attack. In earlier studies^{15, 16} the belief was expressed that another coronary occlusion occurred with greater frequency in patients who regained their hypertension after recovery from the first attack than in those whose blood pressure remained normal. Furthermore, Levine¹ observed that angina pectoris was less frequent and less severe when the pressure did not rise again. On the other hand, Allen⁸ stated that the sooner the pressure returned to previous levels the better the prognosis, and that recovery was usually delayed until previous levels were reached. He believed that when the blood pressure fell from 200, systolic, to 100 or 120, and remained there, the prognosis was guarded until a rise in pressure occurred. Similarly, Palmer¹⁸ stated that the prognosis was better in the hypertensive group; low blood pressure did not seem to protect against another attack. Gross and Engelberg¹⁹ disagreed with these views because they observed no effect of hypertension on duration of life or frequency of heart failure following the attack.

The follow-up observations in our series also show that the height of the blood pressure after the attack did not materially influence the

incidence or severity of angina pectoris or the frequency of subsequent attacks of coronary occlusion or of heart failure (Table XI). However, with regard to each of these factors, the patients who never had had hypertension fared somewhat better than those who were hypertensive either before or after the attack. Thus, it seems that when a patient has hypertension prior to the attack the height of the blood pressure after recovery has no prognostic significance. However, the degree of recovery was generally more complete, and the frequency and severity of heart failure less, among patients who had never had hypertension. This is probably attributable to the lower incidence of cardiac enlargement.

TABLE XI

RELATION OF FOLLOW-UP BLOOD PRESSURE TO SUBSEQUENT ANGINA PECTORIS, HEART FAILURE, CORONARY OCCLUSION, AND DEATH

FOLLOW-UP B.P.	NO.	ANGINA PECTORIS	HEART FAILURE	CORONARY OCCLUSION	DEATH
Hypertensive	140	102 (73%)	37 (26%)	33 (24%)	23 (16%)
Normal					
Previously Hypertensive	25	18 (72%)	5 (20%)	9 (36%)	6 (24%)
Never Hypertensive	56	37 (66%)	11 (20%)	9 (16%)	7 (13%)

DISCUSSION

The incidence of hypertension previous to the attack in our series was probably over 70 per cent, a figure which agrees with that of Palmer,³ namely, 73 per cent. These figures are higher than those usually reported; a survey of the literature^{6, 17} reveals an incidence as low as 30 per cent. One explanation for this discrepancy is that a number of authors have used levels higher than ours as criteria of hypertension; some have accepted only 160/100 mm., whereas others have required 110 diastolic. We believe that our figure, 150/96, is accurate. Another reason for our high figure lies in the fact that many of our patients were followed for a considerable period after the attack, during which time the blood pressure frequently returned to a high level. Confirming this view is the point that, in a series previously reported by us,⁶ in which the blood pressure was considered during the attack only, the incidence of hypertension was 62.4 per cent. It is probable that the actual incidence in our present series was even higher than our figures indicate, for one-third of the hypertensives never regained their high blood pressure.

The incidence of hypertension in persons over 45 years of age in the general population is not known, although it probably is greater than is commonly thought; we have estimated that it is not more than 50 per cent.²⁰ This is lower than that in our series, so that it may be concluded that hypertension predisposes to coronary sclerosis, and, therefore, indirectly to coronary occlusion, which occurs in the natural course of coronary sclerosis. However, there is no reason to assume

a direct connection between hypertension and coronary occlusion, as some authors have done.^{21, 22} They theorize that hypertension, particularly a sudden rise in blood pressure, may produce the intimal hemorrhage which has been shown to be the most common cause of onset of occlusion.²³ We have already pointed out that there is no experimental evidence for this view, and, in addition, we have presented clinical data in a large series of cases to show that coronary occlusion occurs irrespective of external factors, including changes in blood pressure.²⁴ A recent report confirms this view.²⁵ Our pathologic studies also demonstrated that intimal hemorrhages were at least as common among persons with coronary sclerosis without hypertension as among those with it. Intimal hemorrhage in a coronary artery depends merely on the presence of sclerosis; since hypertension is the commonest cause of sclerosis, coronary occlusion is very frequently associated with hypertension. This is particularly true of women, who rarely have coronary sclerosis unassociated with hypertension or diabetes.

Although hypertension plays an indirect role in the pathogenesis of coronary occlusion, it does not affect the course of the disease during or after the attack.^{10, 13} The mortality rate at the time of the attack was the same in the hypertensive and nonhypertensive groups. This may be explained partly by the fact that, although cardiac enlargement and failure are more common in hypertension, the blood pressure rarely falls below 100 mm. in this group, whereas a blood pressure under 100 mm. is common in the nonhypertensive group. A systolic blood pressure below 80 mm., and particularly below 70, is usually of grave prognostic significance,⁹ yet recovery may take place in spite of such a blood pressure at the onset of the attack. When the blood pressure falls below 80 mm., shock is almost always present. However, it was absent in three cases with such hypotension, in spite of the fact that the previous systolic blood pressure had been over 170 in two cases.

Except for the cases in which the systolic pressure falls below 80 mm., the course of the blood pressure during and after the attack is of no definite prognostic significance. Although in general the fall in blood pressure is greater and more rapid when the disease is severe or fatal, mild attacks may be accompanied by a similar fall in blood pressure, and the latter may not fall dramatically with more severe attacks. It is difficult to predict the course of the blood pressure in individual cases. It is apparent, from the number of graphs presented by us, that in many cases the blood pressure trend in coronary occlusion does not conform to one of the main types. In evaluating the blood pressure, therefore, the clinical course of the patient must be carefully considered.

The mechanism of the initial fall in blood pressure in coronary occlusion remains a moot question. It has usually been attributed to peripheral circulatory failure⁹ which is produced reflexly from the

heart and results in pooling of blood in the abdominal organs, with diminution of the venous return to the heart and secondary reduction of the cardiac output. Recently another explanation has been introduced, namely, "cardiac shock."^{26, 27} According to this view there is a primary diminution of cardiac output. Whether or not this factor operates immediately after the onset of the attack, it certainly accounts for continued hypotension after the first few days. Its effect usually lasts about two weeks, by which time the cardiac output returns to normal.²⁸ Thereafter the blood pressure begins to rise toward the level which existed prior to the attack. However, we have shown that one-third of the hypertensives never regain a hypertensive level. The explanation of this is not clear, for the cardiac output is normal and the course of these patients may be as satisfactory as that of patients who regain their hypertension. It is probable that coronary occlusion permanently reduces the peripheral resistance in some cases and not in others.

SUMMARY

The course of the blood pressure before, during, and after the attack has been analyzed in five hundred thirty-eight cases of coronary occlusion.

The incidence of hypertension increased with age.

The blood pressure fell to some extent in every case, although in a few cases the fall was slight. A transitory rise in pressure occurred infrequently at the onset of the attack.

A rapid fall was somewhat more common than a gradual one. Occasionally the fall did not occur until after a week. The lowest pressure was usually reached between the twelfth and twentieth days. In some cases the initial fall was soon followed by a temporary or permanent rise in pressure.

The trend of the blood pressure was similar in the hypertensive and nonhypertensive groups, although a rapid fall was more common among the nonhypertensive patients who died.

The systolic blood pressure rarely fell below 90 mm. in the hypertensive group, but this was common in the nonhypertensive group. When the pressure fell below 80 the patient usually died.

In almost one-fifth of patients with a previous pressure of 200 mm. or more the pressure did not fall below 150 mm.

Two-thirds of the hypertensive patients regained a hypertensive level; in half of these this took place before discharge from the hospital, and, in the remaining half, usually within one or two years.

The height of the blood pressure after the attack did not significantly influence the future course of the patient with respect to subsequent angina pectoris, heart failure, coronary occlusion, or death.

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THE DURATION OF VENTRICULAR SYSTOLE AS MEASURED
BY THE Q-T INTERVAL* OF THE ELECTROCARDIOGRAM,
WITH ESPECIAL REFERENCE TO CARDIAC
ENLARGEMENT WITH AND WITHOUT
CONGESTIVE FAILURE

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VARIOUS factors which may influence the duration of the Q-T interval of the electrocardiogram, aside from heart rate, the blood calcium level, and digitalis have received the attention of few workers. One of the most important clinical conditions, namely, cardiac enlargement, has particularly attracted our attention as needing evaluation in this respect.

Although digitalis somewhat shortens the Q-T interval,¹⁻⁴ which has been reported as prolonged in heart failure,⁷ and a low blood calcium level is associated with considerable prolongation, the Q-T interval varies with the cycle length much more than with any other factor. It is shorter when the heart is rapid and longer when the heart is slow. Fridericia⁸ expressed the relationship in the formula: $Q-T = K \sqrt[3]{C}$, in which C is the cycle length in seconds and K is a constant which he found to be 8.22. Bazett⁹ employed a square root equation in another formula: $Q-T = K \sqrt{C}$, or $K = Q-T \div \sqrt{C}$. It can be seen from the formula that an increase in the Q-T interval, relative to the cycle length, will result in a smaller value for K. Bazett found that K is normally 0.37 for men and 0.4 for women. White and Mudd¹⁰ constructed a scatter diagram relating to the Q-T interval of normal persons, and found that their results agreed closely with the published data of other workers. These various investigators studied the effect of a wide variety of conditions on the duration of the Q-T interval, but there has been a difference of opinion regarding what constitutes a deviation from normal limits. Adams¹¹ used a straight-line formula for calculating the predicted Q-T interval:

$$\text{Male: } Q-T = 0.1536, R-R \text{ } 0.2462$$

$$\text{Female: } Q-T = 0.1259, R-R \text{ } 0.2789$$

More recently, Ashman¹² measured the Q-T intervals of the electrocardiograms of one thousand normal men and women and proposed the logarithmic formula: $Q-T = K \log [10(C + k)]$. C is cycle length in seconds and k is 0.07. According to this formula, K is 0.377 for men and 0.387 for women. Ashman gave the upper normal limits of K as 0.41 for men and 0.42 for women.

*The Q-T interval is the interval from the beginning of the Q wave to the end of the T wave.

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In 1938, White, Jenks, and Benedict¹³ measured the Q-T intervals of the electrocardiograms of a number of circus elephants and found that they were prolonged out of proportion to the heart rates, as compared to the normal human Q-T interval. It was thought that the explanation for this might be found in the immense size of the elephant's heart, with its longer pathways of impulse conduction and its greater bulk of contracting muscle.

This hypothesis suggested that it would be worth while to study the influence of pronounced cardiac enlargement on the duration of the Q-T interval, particularly because such cardiac enlargement in human beings is of serious prognostic importance.

MATERIAL AND METHOD

Two groups of cases were studied. The first group consisted of eleven cases of well-marked cardiac enlargement, with no evidence of congestive heart failure or other complication. The second group of fifteen patients, in addition to cardiac enlargement, also had various degrees of congestive heart failure. The first group was taken from ambulatory patients who presented themselves for routine examination. An attempt was made to select cases of cardiac conditions which produce enlargement affecting primarily one cardiac chamber. In the second group, electrocardiograms were taken soon after admission to hospital. The patients had received no digitalis for at least one month prior to entry. Digitalization was carried out according to the usual routine, and completed in from three days to one week. A second electrocardiogram was taken at the time when the patients had recovered from congestive failure, i.e., from five days to eleven months after the first electrocardiogram.

Only good records with clearly defined QRS waves with well marked T-wave end points were measured. Cases of auricular fibrillation and bundle branch block were excluded. The duration of the Q-T interval of three successive heart cycles was measured in each case, and the results averaged. The cardiac cycle was ascertained by measurements of the Q-Q interval. The Lucas comparator was used for all the measurements; it gives results in ten thousandths of a second, with correct readings to one or two thousandths of a second. The relatively small number of cases studied by us is accounted for by the facts (1) that the great majority of patients with congestive heart failure who came into the hospital had been taking some form of digitalis, (2) that suitable electrocardiograms were not always obtained both during congestive heart failure and after the failure had completely cleared, and (3) that many of the records naturally failed to show sharp end points.

RESULTS AND DISCUSSION

Of the patients with well-marked cardiac enlargement without failure (Table I), six were men and five were women. The average for K, calculated according to Bazett's formula, $K = Q-T \div \sqrt{C}$, was 0.426 (0.421 for the men and 0.431 for the women). Compared with the values given for normal persons by Cheer and Li,¹⁴ which are 0.374 for men and 0.388 for women, these figures represented an appreciable increase above the normal. However, if the figures of Shipley and Hallaran¹⁵ are used, namely, 0.397 for males and 0.415 for females, the departure from normal is not quite so marked. Calculated according to Ashman's formula,¹² $Q-T = K \log [10(C + k)]$, the average K in our

eases was 0.405 (0.403 for the men and 0.408 for the women). This again represents an appreciable increase over the values for normal subjects, which are 0.377 for men and 0.387 for women. It is interesting to compare our figures with those of Ashman, who, in a series of cases of various types of heart disease, found that the average K was 0.405 for men and 0.410 for women.

TABLE I
THE Q-T INTERVAL IN CARDIAC ENLARGEMENT

NO.	SEX	AGE	DIAGNOSIS	X-RAY	Q-Q INTERVAL (SEC.)	Q-T INTERVAL (SEC.)	CONSTANT K (BAZETT)*	CONSTANT K (ASHMAN)†
1	F.	62	Hypertensive	Considerably enlarged heart	0.5805	0.3583	0.470	0.441
2	F.	61	Hypertensive	Enlarged left ventricle	0.8170	0.3586	0.396	0.378
3	M.	71	Hypertensive	Moderately enlarged heart	0.8684	0.4220	0.452	0.434
4	M.	48	Hypertensive and coronary	Enlarged heart	0.8490	0.3809	0.415	0.396
5	F.	26	Rheumatic, aortic stenosis and regurgitation	Considerably enlarged heart	0.6005	0.3092	0.398	0.374
6	M.	70	Hypertensive and coronary; aortic stenosis	Big heart	1.2367	0.4365	0.393	0.376
7	F.	70	Hypertensive and coronary; aortic stenosis and regurgitation	Big heart	0.7470	0.3924	0.453	0.431
8	M.	42	Congenitally bicuspid aortic valve, with scarring	Considerably enlarged heart	0.7461	0.3717	0.430	0.408
9	F.	32	Rheumatic, mitral stenosis	Enlarged, round heart	0.5640	0.3349	0.440	0.418
10	M.	41	Rheumatic, mitral stenosis and regurgitation	Enlarged heart	0.8040	0.3837	0.427	0.407
11	M.	12	Auricular septal defect	Prominent pulm. conus, wide across auricles	0.9128	0.3918	0.410	0.394

*K = $Q-T \div \sqrt{C}$.

†K = $Q-T \div \log [10(C + k)]$.

Although the average value for K in our present series shows that the Q-T interval is definitely prolonged in relation to the heart rate, it must be pointed out that in only six of the eleven cases, or 55 per cent, were the values of K at or beyond the upper limits of normal. It made no appreciable difference whether the enlargement affected the right or

TABLE II
Q-T INTERVAL WITH AND WITHOUT FAILURE

NO.	SEX	AGE	DIAGNOSIS	DURATION OF FAILURE	X-RAY	INTERVAL BETWEEN ELEC- TROCARDIO- GRAMS	CONDITION	Q-Q INTERVAL (SEC.)	Q-T INTERVAL (SEC.)	CON- STANT K (BA- ZETT) *	CON- STANT K (ASH- MAN) †
1	F.	48	Coronary	5 months	Heart enlarged es- pecially left	14 days	In failure	0.7228	0.4246	0.498	0.472
2	F.	56	Coronary	3 months	Enlarged left ven- tricle	15 days	Out of failure	1.040	0.3487	0.341	0.334
3	M.	45	Coronary	1 year	Enlargement all di- rections	7 days	In failure	0.7737	0.4278	0.485	0.462
4	M.	54	Coronary	3 months	Heart enlarged es- pecially left	20 days	Out of failure	0.8273	0.4116	0.452	0.432
5	M.	57	Coronary	4 weeks	Heart enlarged es- pecially left	23 days	In failure	0.6179	0.3577	0.455	0.427
6	M.	52	Coronary	5 weeks	Heart enlarged	14 days	Out of failure	0.8087	0.3834	0.426	0.406
7	M.	56	Hypertensive and coronary	3 months	Heart enlarged both sides	11 months	In failure	0.6837	0.3307	0.400	0.377
8	F.	53	Hypertensive and coronary	3 weeks	Heart diffusely en- larged	3 months	Out of failure	1.0224	0.3506	0.348	0.338
9	M.	56	Hypertensive and coronary	6 months	Heart enlarged, es- pecially left	6 days	In failure	0.7452	0.3491	0.404	0.383
10	M.	54	Hypertensive and coronary	6 weeks	Hypertrophy left ven- tricle	23 days	Out of failure	0.7045	0.3298	0.392	0.371
11	M.	57	Hypertensive	10 days	Heart greatly en- larged, especially left	27 days	In failure	0.7255	0.3653	0.426	0.406
12	M.	55	Hypertensive	1 year	Heart enlarged es- pecially left	17 days	Out of failure	0.5689	0.3546	0.382	0.365
13	M.	49	Hypertensive	5 months	Enlarged, both sides	29 days	In failure	0.7795	0.3713	0.421	0.400
14	M.	47	Hypertensive	3 weeks	Enlarged, both sides	5 days	Out of failure	0.8541	0.3557	0.363	0.348
15	M.	37	Hypertensive	2 months	Heart enlarged es- pecially left	6 days	In failure	0.9295	0.4120	0.428	0.412
							Out of failure	0.7701	0.3697	0.422	0.400
							In failure	0.7147	0.3897	0.462	0.436
							Out of failure	0.8417	0.3681	0.401	0.384
							In failure	0.5992	0.3778	0.488	0.458
							Out of failure	0.6911	0.3269	0.392	0.372
							In failure	1.1101	0.4242	0.402	0.394
							Out of failure	0.9656	0.3822	0.389	0.376
							In failure	0.7819	0.3805	0.430	0.409
							Out of failure	0.7970	0.3590	0.402	0.382
							In failure	0.5748	0.3209	0.425	0.396
							Out of failure	0.5960	0.3297	0.426	0.400
							In failure	0.6872	0.3500	0.422	0.398
							Out of failure	0.7359	0.3770	0.433	0.411
							In failure	0.7463	0.3601	0.418	0.395
							Out of failure	0.8240	0.3424	0.377	0.360

*K = Q-T ÷ √C. †K = Q-T ÷ log [10(C+k)].

left ventricle. When Bazett's formula was used, the average K for the eight cases of left-sided enlargement was 0.426, and, for the three cases of right-sided enlargement, it was also 0.426.

In the second group (Table II), the Q-T interval of the patients with failure showed still more prolongation beyond normal limits. The average K in these cases was 0.438, according to Bazett's formula (0.430 for the men and 0.471 for the women). Cheer and Dieuaide,⁷ using the same formula, found that the value of K was 0.432 for men, and 0.433 for women, with cardiac failure. Their series included relatively few cases of coronary heart disease. Our results in six cases of coronary heart disease and four cases of hypertensive and coronary heart disease confirm their observations. When Ashman's logarithmic formula was used, the average K for our cases of heart failure was 0.415 (0.407 for the men and 0.449 for the women). As compared with the first group, it can be seen that the Q-T interval shows greater prolongation in cases of cardiac enlargement with failure than in those without it.

After recovery from congestive heart failure, the Q-T interval, with two exceptions, exhibited a uniform shortening, relative to the heart rate. In one case there was practically no change, and in the other there was a slight prolongation. The average value for K was 0.396 with Bazett's formula and 0.379 with Ashman's formula, which was about 9 per cent less than during failure. As we pointed out above, the fact that digitalis shortens the Q-T interval has been demonstrated by several workers. Our patients had been given digitalis, and all were taking maintenance doses at the time the second electrocardiograms were taken. Stewart and Cohn¹⁶ showed that digitalis reduces the size of the hearts of normal persons and patients with congestive heart failure. It is therefore interesting to speculate on how much the shortening of the Q-T interval after digitalis is caused by the action of the drug, per se, and how much to the reduction in the size of the heart.

SUMMARY AND CONCLUSIONS

1. In a careful study of twenty-six cases of cardiac enlargement, eleven without, and fifteen with, congestive heart failure, we have found that cardiac enlargement alone, without concomitant congestive failure, produces a significant relative prolongation of the duration of systole, as measured by the Q-T interval of the electrocardiogram, in the majority of cases, taking into due consideration the important factor of heart rate. It made no difference whether the hypertrophy affected primarily the left or the right ventricle.

2. Congestive heart failure, in addition to enlargement, produced a still greater prolongation of the Q-T interval in our cases.

3. After recovery from failure, while the patients were still under the influence of digitalis, the Q-T interval showed a relative shortening.

4. It is possible that cardiac enlargement, with longer pathways of impulse conduction and greater bulk of contracting muscle, is one of the factors responsible for the prolongation of the Q-T interval, and that digitalis may act on the duration of systole chiefly by increasing heart tone, which, in turn, brings about a decrease in the size of the heart.

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THE DEPRESSOR EFFECT OF TISSUE IMPLANTS IN HYPERTENSIVE DOGS

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IN THE course of studies involving the transplantation of kidneys to the necks of hypertensive dogs, we noted that a marked and prolonged depressor effect sometimes occurred as autolysis of the kidney began and an abscess developed at the site of the transplant. This effect could also be produced by subcutaneous implantation of 10 to 15 grams of kidney tissue.¹ To date we have implanted kidney or other tissue in a large number of experiments in dogs with nephrogenic or spontaneous hypertension and in normal dogs.

Blood pressures were recorded on these trained, unanesthetized dogs with the Hamilton manometer according to the technique previously described.² Normal dogs were those which, after a period of training, had a fairly constant arterial pressure of about 150/80 mm. Hg. Dogs with a persistent arterial pressure of 175/95 mm. Hg or more after a prolonged period of training were considered to have spontaneous hypertension. Nephrogenic hypertension was produced by partial constriction of the renal arteries with linen ligatures.³ After the blood pressure of the test animals became stabilized, the various tissues were implanted subcutaneously. Daily recordings of the blood pressure were made until it returned to control levels. This was followed by triweekly recordings for a variable period.

Unless the diastolic pressure fell more than 20 mm. Hg the result was considered negative. When the diastolic pressure decreased more than 20 mm. Hg, but less than 40 mm. Hg, and the fall lasted one or two days, the result was considered slightly positive. An effect greater than this in degree and duration was considered strongly positive. In addition to the blood pressure, the heart rate, rectal temperature, and the general appearance of the animals were observed.

The tissues were implanted subcutaneously in the lumbar region, and the subcuticular fascia and skin were stitched over the implant. Asepsis was not maintained.

The following substances were used: (1) Fresh dog, rabbit, beef, and pig kidney, 10 to 30 grams;* (2) fresh dog heart, liver, or spleen, 10 to 30 grams; and (3) 10 c.c. of egg yolk or 1 to 3 grams of infusorial earth in saline suspension.

RESULTS

The effects of the various implants and injections are briefly summarized in Tables I, II, and III. Abscesses developed in nearly every instance, began to drain on the second and third day, and were usually entirely healed by the seventh day. The rectal temperature was raised

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TABLE I

EFFECT OF VARIOUS TYPES OF SUBCUTANEOUS IMPLANTATIONS ON THE ARTERIAL PRESSURE OF DOGS WITH NEPHROGENIC HYPERTENSION, AS JUDGED BY THE EXTENT AND DURATION OF THE FALL IN BLOOD PRESSURE*

TYPE OF MATERIAL IMPLANTED	BLOOD PRESSURE RESPONSE†			DEATH OF ANIMAL	TOTAL
	NONE	SLIGHT	DEFINITE		
Fresh dog kidney	21	7	14	2	44
Fresh dog kidney in small amount (1 Gm.)	4				4
Fresh rabbit kidney	4				4
Beef kidney	5	1	1		7
Pig kidney	7				7
Fresh dog heart	8	1	1	2‡	12
Fresh dog liver	7	4	1		12
Fresh dog spleen	2				2
Egg yolk	5				5
Infusorial earth	3				3

*In practically all cases fever occurred; the rectal temperature rose from about 101.5° C. to 103.5 or 105° C., usually within twenty-four hours. This was associated with cardiac acceleration. The fall in blood pressure, when it occurred, usually was not manifest until the third day, when the temperature was again approaching normal. The fever occurred not only in animals in which the blood pressure fell, but also in those in which it did not.

†Classification of response described in text.

‡In both of these dogs the blood pressure was lowered toward normal levels for some time before the animals died.

TABLE II

EFFECT OF VARIOUS TYPES OF SUBCUTANEOUS IMPLANTATIONS ON THE ARTERIAL PRESSURE OF SPONTANEOUSLY HYPERTENSIVE DOGS, AS JUDGED BY THE EXTENT AND DURATION OF THE FALL IN BLOOD PRESSURE*

TYPE OF MATERIAL IMPLANTED	BLOOD PRESSURE RESPONSE* .			DEATH OF ANIMAL	TOTAL
	NONE	SLIGHT	DEFINITE		
Fresh dog kidney	2		8	1	11
Fresh dog heart muscle	2				2
Fresh dog liver		1			1
Egg yolk	1				1
Infusorial earth	4	1			5

*See footnotes of Table I

TABLE III

EFFECT OF VARIOUS TYPES OF SUBCUTANEOUS IMPLANTATION ON THE ARTERIAL PRESSURE OF NORMAL DOGS, AS JUDGED BY THE EXTENT AND DURATION OF THE FALL IN BLOOD PRESSURE*

TYPE OF MATERIAL IMPLANTED	BLOOD PRESSURE RESPONSE*			DEATH OF ANIMAL	TOTAL
	NONE	SLIGHT	DEFINITE		
Fresh dog kidney	8				8

*See footnotes of Table I

from the normal of 101.5 to 103.5 or 105° C. within twenty-four hours, and returned to normal in a day or two. The animals seldom manifested any particular depression, but frequently showed discomfort which was apparently caused by the inflamed and tender infected areas in the region of the tissue implantation. On occasion, however, the reaction was more severe, and several animals died two to six days after

implantation. There was no significant difference in these general reactions among the various groups of animals nor with the various types of implants.

In contrast to the similarity of these general effects, certain differences in the blood pressure response were apparent. In none of the eight experiments on normal dogs was any significant depressor effect noted (Table III). With dog kidney implants a definite depressor effect was obtained in fourteen of forty-four trials on dogs with nephrogenic hypertension and eight of eleven trials on spontaneously hypertensive animals. This is in sharp contrast to the results obtained with implantation of other tissues in hypertensive dogs, in which only one of fourteen trials with beef or pig kidney, one of fourteen with dog heart, and one of thirteen with dog liver gave a definite depressor effect. In none of the six trials with egg yolk and the eight trials with infusorial earth was a definite depressor response obtained in the hypertensive dogs.

DISCUSSION

Since our preliminary note on the effect of subcutaneous implantation of kidney tissue, the experiment has been repeated with modifications by other investigators. It has been reported⁴ that, if special precautions are taken to avoid infection, abscess formation does not occur and the blood pressure does not fall. In rats, a reduction in blood pressure follows abscess formation, but in this animal the depressor effect appears to be nonspecific, for it occurs with implants of spleen and liver, as well as kidney.⁵ Our results indicate that in the dog the reaction appears to be more specific for kidney. It would appear that, in the process of abscess formation after implantation of dog kidney, some reaction occurs which tends to reduce both nephrogenic and spontaneous hypertension. The results in spontaneous hypertension are of particular interest, for it may be more analogous to human essential hypertension than is nephrogenic hypertension.

Since the fall in blood pressure occurs on the third day, when the fever and the reaction to the abscess are on the decline, and since the depressor effect persists in some experiments for many days after the abscess has completely drained and healed, the effect probably cannot be solely the result of fever or infection. The occurrence of fever in most of the animals whose blood pressure did not fall also suggests that any fall in blood pressure is not due simply to the vasodilator effect of fever. Furthermore, we have seen a number of instances of severe infection, such as pneumonia and postoperative abscesses, in our hypertensive dog colony without changes in blood pressure.⁶ Distemper, however, frequently caused the pressure to fall for some time.² Furthermore, a depressor effect from the injection of nonspecific materials, such as pyrogenic inulin, typhoid vaccine, etc., has been reported,^{7, 8} and the blood pressure of hypertensive human subjects may fall during fevers, infections, and intoxications.⁷ For example, it has been reported

that, during the induction of malaria in hypertensive patients, the blood pressure may fall and remain at a normal level for a period of days, even after the fever has subsided.⁹ It was further observed that even when the pyrogenic reaction is prevented by amidopyrine, the depressor effect in hypertensive subjects is still present.⁷

A number of extracts of plants and animal tissue have been advocated for the treatment of hypertension; each has had its vogue, but none has been widely accepted.^{10, 11} Kidney extracts have been employed for sundry purposes, including the treatment of hypertension, but until recently without rational or experimental basis. In some of the earlier work, in which the renal extracts were given intravenously, the effect on the blood pressure was probably a peptone reaction.

Recent developments in the study of hypertension have established a more rational basis for the use of kidney extracts in the treatment of the disease.^{12, 13} Although these studies are in accord that an anti-depressor effect may be produced by the administration of kidney extracts, the concepts advanced as to the cause of the fall in blood pressure do not agree. Further, the methods of extraction of the kidney in the various studies are different. The extracts are still crude and require large quantities of kidney to furnish relatively small amounts of depressor material. At present there is no unanimity concerning the nature of the principle.¹⁴ For example, one group¹³ has found that it follows the protein fraction and is not an ultrafiltrate, whereas another,¹² using similar methods of preparation, reports that it is an ultrafiltrate and not a protein. The possibility that in many cases the fall in blood pressure may be spontaneous, or the result of more complete control of the patient, has not been definitely ruled out. In animals similar fluctuations in blood pressure are frequently observed, and may even occur in well-trained dogs with severe hypertension.⁶ Recent studies^{7, 8, 9} on the depressor reactions brought about in hypertensive subjects by nonspecific pyrogenic substances raise some doubt as to the specificity of the renal extracts previously employed.

Our own results may be ascribed to a nonspecific reaction of a similar nature. However, the absence of a depressor response in the normal dogs with kidney abscesses indicates that, in our experiments, there was no general depressor effect which might result from conditions in infection that lead to peripheral vascular collapse. We have previously noted that the factors which maintain hypertension and normal blood pressure are different, and it is well known that changes in the blood pressure, especially downward deviations, are resisted by numerous mechanisms. Normal animals appear to show a greater resistance toward depressor effects than hypertensive animals. We are, however, inclined to the view that, although this factor is of importance, it cannot be the sole cause of the difference in response between normal and hypertensive animals, for a survey of depressor actions in general shows that they operate on normal as well as hypertensive subjects. Thus, for

example, we have found that the depressor effect of late pregnancy occurs in normal as well as in hypertensive animals.⁶

It is still possible that our results can be interpreted as a nonspecific reaction operating under the peculiar conditions of the hypertensive animal. It has been shown⁷ that the pyrogenic reaction, even in the absence of fever, leads to renal hyperemia. This renal hyperemia will reduce the ratio of ischemic to normal kidney tissue, and thus allow a reduction in blood pressure.² This would presuppose a renal mechanism in the spontaneous hypertension of the dog, and this is not yet established. If renal hyperemia is the cause of a nonspecific reduction in hypertension, our results would suggest that the liver, spleen, and heart abscesses liberate more of the effective substances than egg yolk and infusorial earth abscesses, and that kidney abscesses liberate even more. It is possible that these substances may act on other organs which participate in the hypertensive process, or may act directly on the chemical mediator of hypertension, but these possibilities will not be discussed here.

However, the alternate view has not been excluded that in abscesses produced by the implantation of fresh dog kidney a specific antihypertensive principle is elaborated or liberated. If this be so, our work indicates that 10 to 30 grams of kidney may be sufficient to produce enough material to lower the blood pressure of hypertensive dogs. To date, other workers have required large amounts of kidney for the production of their principles. In this case more potent preparations of antihypertensive principle are possible.

SUMMARY

1. The subcutaneous implantation of 10 to 30 grams of fresh dog kidney leads to abscess formation in forty-eight to seventy-two hours and frequently results in a reduction of the blood pressure of dogs with nephrogenic or spontaneous hypertension.

2. In normal dogs similar abscess formation has no appreciable effect on blood pressure.

3. Abscesses produced by implantation of fresh muscle, liver, or spleen have little or no effect on the blood pressure of hypertensive dogs.

4. The significance of these results is discussed.

We are indebted to Dr. M. Sokolow and Miss L. Friedberg for assistance in the early experiments of this study.

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Clinical Reports

A CASE OF BUERGER'S DISEASE IN AN OLD WOMAN

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THE occurrence of thromboangiitis obliterans in an old woman is sufficiently infrequent to warrant recording it.

CASE REPORT

M. C., a 68-year-old white woman, came under observation Oct. 28, 1941. Three weeks previously she had been suddenly seized with severe pain in her right leg, followed by coldness and numbness of both feet. Two weeks later intense burning pain appeared in the right second toe, and the toe turned blue. Prior to the onset of her present illness she had never had any symptoms which could have been attributed to vascular disease of the lower extremities. She had never smoked and had never suffered from any form of superficial phlebitis.

Examination.—The patient was in evident distress. No pulsation was palpable in the dorsalis pedis, posterior tibial, or popliteal artery in either leg. Excellent pulsations could be felt in both common femoral arteries. Oscillometric readings were zero up to the level of the knees. At a room temperature of 24.0° C., the surface temperature of the great toes was 25.0° C. After the administration of 50 mg. of procaine intrathecally, anesthesia of both feet occurred, but the surface temperatures rose only 1.3 degrees. There was extreme pallor of both feet on elevation, and the right foot was edematous. There was ulceration of the right second and left fourth toes. The ulcerated right second toe was exceedingly sensitive to the slightest manipulation, and was in a state of impending gangrene. There were no areas of acute or healed superficial phlebitis. She presented clinical evidence of generalized arteriosclerosis. Her blood pressure was 238/134.

The blood Wassermann reaction was negative. The erythrocyte count was 3,800,000, and the hemoglobin was 67 per cent. The albumin/globulin ratio was 4.1/4.3. The sugar and nonprotein nitrogen levels in the blood were 129 and 28 mg. per cent, respectively. The spinal fluid was normal.

A diagnosis of bilateral, acute thrombosis of an arteriosclerotic popliteal artery was made.

Within twenty-four hours of her admission to the hospital the right second toe had become frankly gangrenous. In an attempt to alleviate the now intractable pain, an adventitial stripping of the superficial femoral artery and ligation of the accompanying vein were performed. At the time of operation I was impressed by the absence of significant atheromatous involvement of the wall of the occluded femoral artery. The next morning there was a distinct diminution in pain and sensitivity to manipulation in the gangrenous toe. However, the gangrene continued to spread. By the tenth hospital day the entire foot had become gangrenous, pain had recurred, and a thigh amputation was performed as a life-saving measure. However, that evening the left foot became suddenly gangrenous, and three days later the patient died.

The following is a detailed report of the microscopic examination of sections taken from the arteries of the amputated leg. The description is by Dr. F. Preuss, of the Laboratory of Pathology at Mt. Sinai Hospital.

Popliteal Artery and Vein.—The lumen of the artery is occluded by fairly dense connective tissue containing a large number of fibroblasts and mononuclear cells. A few small vascular spaces lined with epithelium and filled with erythrocytes are seen. These apparently represent areas of recanalization. The media shows a diffuse infiltration with lymphocytes and mononuclear cells. The intima and internal elastic lamella are indistinct. The adventitia is composed of very dense connective tissue which is infiltrated with lymphocytes and mononuclear cells; it contains numerous vasa vasorum which exhibit similar chronic inflammatory changes. The popliteal vein shows similar inflammatory changes. The intima is thickened by granulation tissue. The media is interrupted by connective tissue showing numerous fibroblasts and round cell infiltration. The adventitia presents a picture similar to that of the adventitia of the artery. The artery and vein are adherent to each other by dense inflammatory connective tissue.

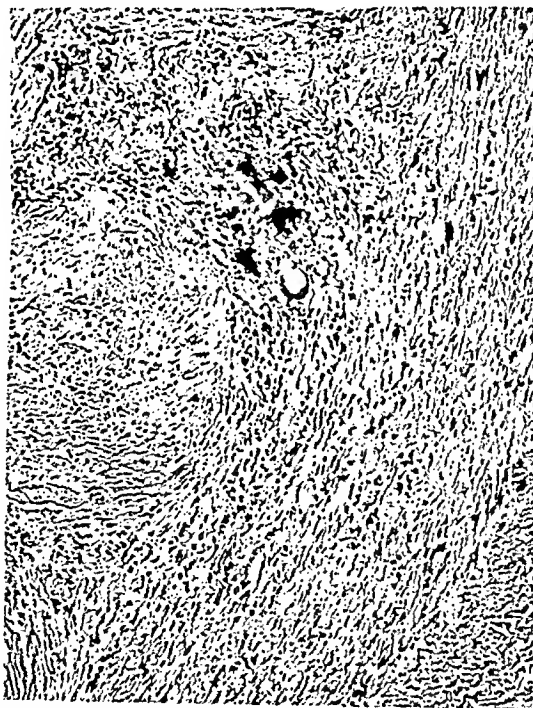


Fig. 1.—Posterior tibial artery. (Dr. F. Preuss)

The lumen of the artery is occluded by cellular granulation tissue containing only a few small capillary vascular spaces. The internal elastic lamella is indistinct and fragmented. The media is markedly infiltrated with lymphocytes and monocytes. Several giant cells are present, indicating a chronic and subacute inflammatory process. There is also increased vascularity of the media.

Posterior Tibial Artery.—See Fig. 1.

Posterior Tibial Vein.—See Fig. 2.

Anterior Tibial Artery and Vein.—See Fig. 3.

Final Diagnosis: Thromboangiitis obliterans (Buerger's disease).

In addition to the fact that the patient was a woman, the interesting point is that she reached the age of 68 years before the peripheral vascular disturbance became manifest clinically. This attests that a

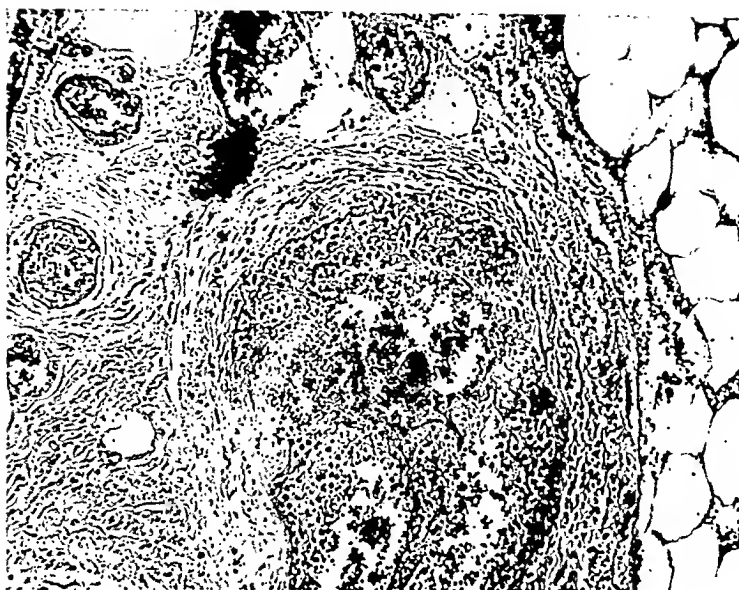


Fig. 2.—Posterior tibial vein. (Dr. F. Preuss)

The lumen is occluded by an apparently recent, red thrombus, consisting mainly of erythrocytes and a few threads of fibrin. The endothelial lining of the intima is stripped off in places. The media shows diffuse infiltration by polymorphonuclear leucocytes. There are also a marked periphlebitis and an increase of vasa vasorum in the adventitia.

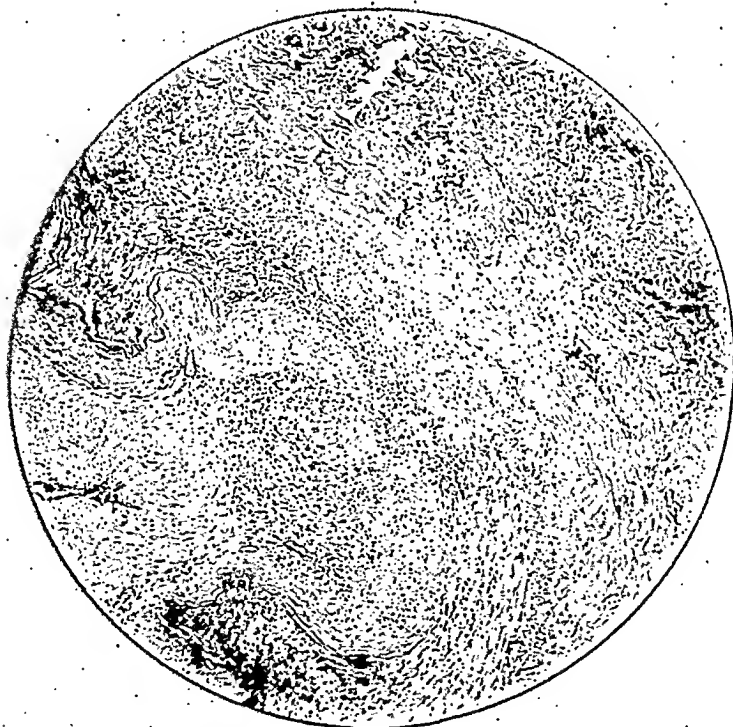


Fig. 3.—Anterior tibial artery and vein. (Dr. F. Preuss)

The lumen of the artery is reduced to a slit-like space by fibrous tissue which in one sector, shows a marked cellular reaction. The internal elastic lamella is recognizable only in the upper sector. There is moderate cellular infiltration of the media. In the upper right-hand corner the small residual lumen of the vein is seen. Artery and vein are matted together tightly by old granulation tissue. The line of cleavage cannot be made out.

remarkably effective collateral circulation may develop in cases of thromboangiitis obliterans without the benefit of therapeutic assistance. In line with this observation is the case of a 65-year-old man with Buerger's disease whom I saw recently. In this instance the first clinical evidence of the vascular disability was also the sudden appearance of pain in the leg and foot, followed by gangrenous ulceration. Microscopic examination of the arteries in the amputated leg revealed lesions characteristic of long-standing thromboangiitis obliterans, with recent, major thrombosis involving the popliteal and lower femoral artery.

The author acknowledges his indebtedness to Dr. S. S. Sidenberg, the attending physician in this case.

DISSECTING ANEURYSM OF THE ABDOMINAL AORTA

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IN A RECENT paper on dissecting aneurysm, Rogers¹ remarks that, until 1933, only six cases of this condition had been discovered ante mortem. Since then, thirty-four additional cases have been reported. In view of the many outstanding manifestations of this disease, it is remarkable that more cases have not been reported. The following case is presented to emphasize the important signs and symptoms of this disease, and because it is the second case in which a dissecting aneurysm beginning in the abdominal aorta has been diagnosed before death. It is interesting that the diagnosis in this case was made by an intern, and overlooked by men of far greater experience. This is not a criticism of these men, but rather an indication of the lack of awareness of the average practitioner to the clinical features of dissecting aneurysm.

CASE REPORT

The patient was a white man, 64 years of age, who was admitted to the hospital because of severe, recurring radiating pain of over three years' duration. For more than thirty years the patient had suffered from vague abdominal distress, but in the preceding three years a new symptom became prominent. The symptom was pain, described as agonizing and viselike, which always began in the epigastric or lower substernal region, radiated upward to involve the entire chest and back, and then spread down the arms as far as the finger tips and upward to the neck and head as far as the vertex. This radiation was fairly constant, and the distribution was symmetrical. At first the patient suffered at irregular intervals, especially, but not always, after strenuous exertion. At the beginning of the illness the pain lasted only a few minutes, but later it occurred with increasing frequency and severity, and lasted as long as thirty minutes. There were intervals of days or even weeks when this agonizing pain did not occur. The patient knew of nothing that would relieve the pain, but he remarked that he tried to calm the "torture" by compressing and rubbing his abdomen and chest; however, this produced no relief. For eighteen months a mass in his abdomen had been evident, and was increasing in size.

The past history revealed that the patient had had left-sided, spontaneous hydropneumothorax from a "ruptured emphysematous bleb" which disappeared without complications. There was also a history of chronic atrophic gastritis, with achylia gastrica, bilateral direct inguinal hernia (not operated on), and some "duodenal disturbance" of unknown origin. Three years earlier he had been examined at the Mount Sinai Hospital of New York City. The roentgenologic reports from that institution revealed that he had a large tortuous aorta, but no diagnosis of aneurysm was made. Hypertension and severe arteriosclerosis were also diagnosed at that time.

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Physical examination revealed a tall, thin, elderly, and chronically ill white man. The head was essentially negative, as were the eyes, ears, and nose. He had pyorrhea alveolaris and many carious teeth. The chest was asthenic and the ribs were very prominent. A marked depression at the lower portion of the sternum, probably occupational in origin, was noted. The patient was an architect, and had worked over a draftsman's board for years. The lungs were normal. The heart was enlarged to the left (approximately 2 cm. beyond the left midclavicular line, fifth intercostal space); the rhythm was normal, and auscultation revealed a systolic and a diastolic murmur in the aortic region which were transmitted upward and downward along the right sternal margin. The pulse rate was 76, and the pulse was full and strong. His blood pressure was 250/170 in the left arm and 256/174 in the left leg. Within the abdomen, just below the epigastric region, there was a very interesting tumor about the size of a grapefruit. The tense mass, a practically immovable tumor and with no expansile pulsation, extended below and to the left, and above and to the right of the umbilicus. No thrill was palpable, but there seemed to be a slight, inconstant systolic murmur. The abdominal wall was very thin, and there was a direct inguinal hernia on each side. The arteries were very hard and tortuous, particularly the femorals, which were pipelike and at least 2 cm. in diameter, and could be easily palpated as they coursed over the pubic rami. The other systems were essentially negative.

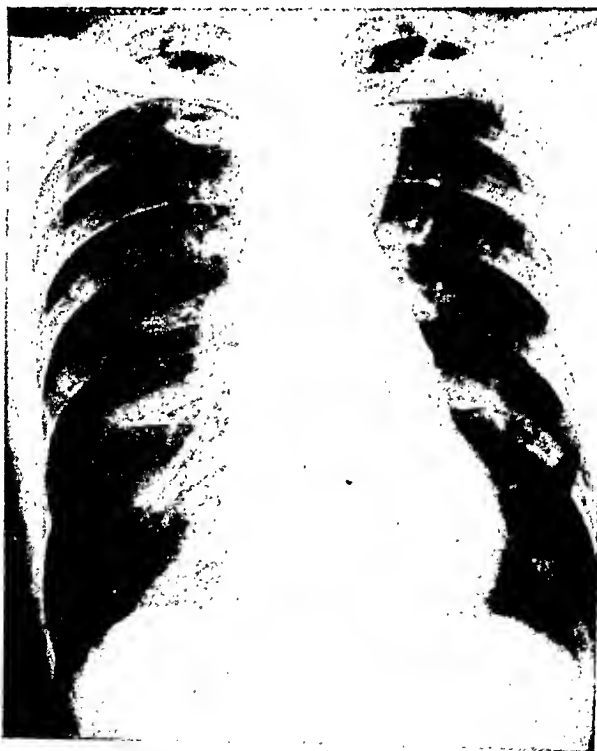


Fig. 1.

At the time, the provisional diagnosis was "Aneurysm of the abdominal aorta, arteriosclerotic in origin and dissecting and saccular in type."

Laboratory Examination.—The leucocyte count was 7,300, with a normal differential count. The erythrocyte count was 4,320,000, with 86 per cent hemoglobin (12.6 Gm., Sahli). The Kolmer-Wassermann reaction was negative. The urine showed an occasional hyaline cast. Electrocardiographic studies, unfortunately, were not made. Roentgenologic examination included stereoscopic and oblique

chest films and gastrointestinal study. The latter showed external pressure on the lesser curvature of the stomach. The chest roentgenograms showed (Figs. 1 and 2) enlargement of the cardiac shadow, especially of the left ventricular portion, and a greatly dilated and tortuous aorta which took the shape of the letter S; the arch was represented by the upper half of the letter, and the thoracic portion by the lower half. The lateral deviation from the midvertebral line to the left lateral border was 9 cm. at the level of the ninth dorsal vertebra. In this region the aorta showed its greatest transverse diameter (4 to 5 cm.). These observations were essentially the same as those made at Mount Sinai Hospital.



Fig. 2.

Subsequent Course.—During the first five days of hospitalization the patient was up and about. He complained only of a constant, dull, abdominal pain. Never did he have the severe pain mentioned in the “present illness.” The preoperative diagnosis of the surgeon was “pancreatic or peritoneal cyst or possible aneurysm of the abdominal aorta.” The last diagnosis, in view of the operation performed later, apparently held little favor. At operation, “an aneurysm was found just above the bifurcation of the aorta, about 8 to 10 cm. in diameter, with one small sacculation at its right border, on the lateral aspect.” No surgical procedure was attempted on this lesion. On the day after the operation the patient complained of pain in the abdominal wound. His second day was uneventful, but, on the night of the third postoperative day, at 11 o'clock, he complained of a sudden, severe pain in the abdomen, and died before the intern arrived.

Post-Mortem Examination (performed by Dr. W. Cook).—Only the main gross autopsy observations in regard to the aneurysm and arterial system are discussed. When the abdominal cavity was opened it was found to contain a great deal of coagulated blood. The abdominal aorta presented a large rent at its beginning; this extended downward several centimeters, beyond the level of the renal vessels. The entire vessel, though collapsed post mortem, had been diffusely enlarged, and

anterolaterally the wall showed sheath dissection from the region above the renal vessels to just above the bifurcation. The adventitial portion of the aneurysm was over 10 cm. in diameter, and contained a large laminated thrombus; its proximal level communicated with the lumen of the aorta through a large opening. The internal surface of the aorta showed marked atheromatous degeneration and ulceration throughout, especially in the abdominal portion, and also some ulcers 2 to 3 cm. in diameter, with deep overhanging walls filled with thrombi and lipid material. The thoracic aorta was markedly dilated and tortuous, and the lower half extended far into the left thoracic cage. There was also marked arteriosclerosis involving the muscular arteries. Other important associated abnormalities were left ventricular hypertrophy and nephrosclerosis.

COMMENT

Excellent discussions of the etiology and pathology of this condition have been presented in other papers. In this case, the outstanding etiologic factors were arteriosclerosis, hypertension, and probably occupational trauma. Repeated pressure of the draftsman's board over a period of many years directly against the abdomen and sternum and indirectly on the atheromatous aorta might have been an important factor in the development of the aneurysm; however, one must admit that it might have been coincidental. This case again emphasizes the importance of severe oppressive pain with radiation. It is difficult to explain the wide distribution of the pain in this case (probably a great deal of it arose from the arch and thoracic aorta), but radiation of pain is one of the most common symptoms, and occurs in practically every case, with the exception perhaps of some of the more fulminating lesions.

Dissecting aneurysms rarely reach the dimensions of the one described, but in this regard there was a similarity to Bahrddt's² case, in which there was a pulsating tumor, the size of a hen's egg, above the umbilicus.

This case also shows that dissecting aneurysm is not necessarily an "acute catastrophe," as many are inclined to believe. The case of Rogers¹ and several others support this fact, and the pathologic reports are confirmatory. From the history, one might say that the dissection probably began at least three years prior to the patient's death.

SUMMARY

A case of aneurysm of the abdominal aorta, diagnosed ante mortem, is reported; this is the thirty-fifth dissecting aneurysm, and the second beginning in the abdominal aorta, on record.

The author wishes to thank Dr. Roberto for the roentgenograms, and Dr. Buel Latcher. The patient was originally under the care of Dr. Latcher, who, from the beginning, agreed with the author's diagnosis.

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INTRAUTERINE TRAUMATIC LESIONS OF THE HEART

REPORT OF A CASE, WITH AUTOPSY

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NONPENETRATING injuries of the chest wall which produced cardiac lesions in adults have been reported by Kahn and Kahn,¹ Kissane, Fidler, and Koons,^{2, 3, 4} Bright and Beek,⁵ Beek,⁶ and Moritz and Atkins.⁷ These reports establish trauma to the heart as a cause of death in nonpenetrating injuries of the chest wall, and are supported by anatomic and experimental evidence. Intrauterine lesions of the heart produced by trauma to the maternal abdomen have not been reported. The following case is presented to illustrate this condition.

CASE REPORT

The patient, a 17-year-old primigravida, was under obstetrical care during her entire prenatal period, during which time her weight gain had been 18 pounds. Three days before her estimated date of confinement she had her last prenatal examination, at which time the baby was alive, as evidenced by fetal motion and fetal heart tones in the left lower quadrant at the rate of 136 per minute. Her entire prenatal course had been uneventful; the blood pressure was within normal limits, the urine on all examinations was negative for albumin and sugar, and the blood serologic reactions were negative.

Six hours after her last prenatal examination she was in a severe automobile accident. The car in which she was riding as a passenger was struck from the left side by another car. She was thrown a distance of about ten feet from the car through the right car window, and struck her abdomen on the curb. She was taken to a hospital for treatment of lacerations of the forehead and right hand and severe contusions of the abdominal wall. In the accident room of this hospital it was noticed that the fetal motion and heart tones were absent. She was kept under observation at this hospital for two days, and, on the third day, which was her estimated date of confinement, she was brought to White Cross Hospital.

Upon admission, the uterus was enlarged to the size of a full-term pregnancy, but death of the fetus was evidenced by the absence of fetal motions and heart tones. The uterine contractions were strong and regular, and occurred at three-minute intervals. Rectal examination showed that the cervix was effaced, was dilated 2 cm., and that the head was at the level of the ischial spines. The labor was conducted under sodium amytal and scopolamine analgesia. Delivery was accomplished by prophylactic forceps extractions, preceded by a right mediolateral episiotomy under nitrous oxide-ether anesthesia. The baby was a full-term still-born female, and weighed 7 pounds. The duration of labor was eleven hours and thirty minutes; the first stage lasted ten hours and forty-five minutes, the second stage, thirty-five minutes, and the third stage, ten minutes.

Autopsy.—Autopsy was performed on the stillborn child two hours after birth. The body was that of a well-developed and well-formed female; it measured 48 cm.

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in length and weighed 7 pounds. There were no malformations or deformities, the skin was intact and of normal color, and the usual short portion of umbilical cord was attached and slightly dried.

Upon opening the abdomen the peritoneum was found to be smooth and glistening and free from petechiae or ecchymoses; there were approximately 5 c.c. of a clear amber fluid free in the peritoneal cavity. The various viscera were in their normal positions, and the liver extended the usual distance below the right costal margin. There was no evidence of rupture of the liver; no subcapsular hematomas were found, and the cut surface of the liver was normal. The gall bladder, pancreas, and spleen were normal. The kidneys, ureters, and urinary bladder were entirely normal. Both adrenal glands were normal for a newborn. The pelvic viscera were normal. The lymph nodes of the mesenteric and retroperitoneal groups were not enlarged. There was no retroperitoneal hemorrhage, and the lumbar spine and bony pelvis were normal.



Fig. 1.—Lungs, pericardium, and diaphragm, showing hemorrhages over the external pericardial surface and mesial portions of the adjacent lungs.

Upon opening the thoracic cavity by elevation of the sternum, both pleural cavities were found to contain approximately 10 c.c. of bloodtinged fluid. The pericardial sac was rounded and widened to a transverse diameter of $3\frac{1}{2}$ cm. The thymus was of the usual size and shape, with the right lobe extending downward as a thin prolongation just over the upper portion of the pericardial sac. There was no evidence of hemorrhage into the thymus or mediastinum. There was no fracture or dislocation of the ribs, sternum, or dorsal spine, but on the lateral surface of the right parietal pleura there were several small petechial areas.

The lungs were unexpanded, and, over the pleural surfaces of the middle and upper lobe of the right lung, especially over its mesial surface, there were scattered areas of petechiae. There were similar areas in similar positions over the mesial surface of the left lung. Cut sections of the lungs showed no evidence of expansion and no interstitial hemorrhage, and the trachea and bronchial tree were free and patent.

The external surface of the pericardial sac presented multiple areas of fresh hemorrhage, extending on the right side down to the level of the diaphragm (Fig. 1). The pericardial sac was found to contain a markedly increased amount of hemorrhagic fluid. On the inner surface of the pericardial sac there were multiple areas of hemorrhage similar to those on its external surface. No gross tears of the pericardium were found. The heart presented multiple areas of hemorrhage over its anterior surface, and, involving the descending branch of the left coronary artery and vein for a distance of 2 cm., there was an area of hemorrhagic extravasation measuring 5 mm. in diameter (Fig. 2). Over the posterior surface of the heart, extending downward along the distribution of the descending rami of the circumflex artery, there were similar areas of hemorrhagic extravasation. Similar hemorrhagic material was found along the course of the right coronary artery. No contusion of the myocardium was apparent from the epicardial surface. Dissection of the coronary arteries failed to demonstrate a point of actual vessel rupture; the hemorrhage described above appeared as a dense extravasation into the epicardium. The coronary arteries showed no evidence of congenital sclerosis. Upon opening the heart, the various valves and chambers were found to be normal, and there was no evidence of endocardial hemorrhage or myocardial contusion.



Fig. 2.—Lungs and heart after opening the pericardial sac, showing hemorrhage over the epicardial surface and along the left coronary vessels.

Examination of the head showed no lesions of the scalp or calvarium, the dura and arachnoid were normal and free from hemorrhage and tears, and the brain was grossly normal.

The anatomic diagnosis was traumatic heart disease, characterized by pleural, pericardial, and epicardial hemorrhage, with hemopericardium, hemothorax, and unexpanded lungs.

Microscopic sections of the lungs showed no expansion, no interstitial hemorrhage, and occasional alveoli filled with coagulated fluid; the hemorrhage on the pleura appeared as infiltrating hemorrhagic extravasations elevating and sometimes penetrating the pleura.

Microscopic sections of the pericardial sac showed hemorrhagic infiltration of the fibrous external tissue, without tears; on the inner surface, this hemorrhage elevated and penetrated the endocardial lining. Sections of the heart itself showed extensive extravasation of fresh blood cells throughout the epicardial tissue about the coronary arteries, with hemorrhagic invasion of the adventitial, and, in some cases, of the external medial, portions of these arteries and veins. The inner medial layers and intima of these vessels appeared normal in the various sections. There was only slight invasion of the adjacent myocardium by this recent hemorrhage. There was no evidence of organization in any of the hemorrhagic areas. Sections of various other organs and tissues showed no pathologic changes.

The final diagnosis was traumatic heart disease characterized by acute hemorrhagic extravasation into the epicardium along the course of the coronary vessels, additional traumatic hemorrhages into the pericardium and pleura, hemopericardium, hemothorax, and death in utero with unexpanded lungs.

DISCUSSION

The cardiac, pericardial, and pleural lesions in this case were entirely comparable, and were similar to those in previously published cases of traumatic heart disease. Epicardial lesions are more common than lesions of the myocardium and pericardium. Hemopericardium is also frequent in this condition. The trauma manifest in this heart and pericardium would be considered quite extensive even in the adult heart, so that the hemorrhage could be properly designated as massive.

The fact that there was an apparently normal heart and baby a few hours before the injury, the history of a severe, direct blow to the maternal abdomen and uterus, and the discovery that the baby was dead soon after the injury establish a sequence of events which is entirely compatible with the autopsy observations.

SUMMARY

A case of intrauterine cardiac injury which was produced by a non-penetrating blow to the maternal abdomen and resulted in the death of the fetus is reported.

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Abstracts and Reviews

Selected Abstracts

Friedman, M., and Kaplan, A.: Studies Concerning the Site of Renin Formation in the Kidney. IV. The Renin Content of the Mammalian Kidney Following Specific Necrosis of Proximal Convoluted Tubular Epithelium. *J. Exper. Med.* 77: 65, 1943.

The admission of tartrate to adult rabbits was found to produce in some of them, a profound and widespread necrosis of the proximal convoluted tubular epithelium without affecting the other portions of the nephrons.

The markedly damaged kidneys were found to be almost completely devoid of pressor substance (renin), indicating that in the mammalian kidney, the epithelium of the proximal convoluted tubules is concerned in the formation or storage of renin.

AUTHORS.

Dauber, D. V., and Katz, L. N.: Experimental Cholesterol Atheromatosis in an Omnivorous Animal, the Chick. *Arch. Path.* 34: 937, 1942.

Twenty-four 10-day-old cockerels were divided into two equal groups. One group was fed an adequate diet for fifteen weeks. The second group was placed on the same diet plus 2.5 to 5 per cent cholesterol in cottonseed oil. In none of the control cockerels did vascular lesions develop. In seven of the twelve cholesterol-fed birds (the remaining five dying within eight weeks) atheromatous deposits developed in the aorta. Of these seven chicks, three had intimal atheromatous lesions in the coronary arteries with resultant narrowing of the vessel lumens; two of the seven showed similar changes in the splenic arteries. The hearts of the cholesterol-fed birds weighed slightly more in proportion to the body weights than did those of the control series.

The chick is an omnivorous animal in which experimental atheromatosis can be readily produced by feeding a high cholesterol diet. The induced arterial lesions resemble the earliest spontaneous atheromatosis which develops with advanced age in chickens.

AUTHORS.

Krafka, J., Jr.: A Heretofore Unrecognized Mechanical Principle Effective in Aortic Sclerosis. *Arch. Path.* 34: 965, 1942.

By using the formulas of mechanical engineering for stress in the walls of thin-walled cylinders, it is possible to relate stress in the aortic wall to blood pressure values.

Calculated values for systolic and diastolic pressures fall well within the hollow portion of the exponential curve obtained by stretching strips of aortas on the scirigraph.

Percentage extensibility of the strips of aortas within the stress equivalents for systolic and diastolic pressures is consistent with the normal stroke volume considerations.

With aging, fibrosis, and sclerosis, there is a tendency to convert the plastic cylinder into a rigid one. A redistribution of force vectors accordingly follows the rivet rule, and hence a normal blood pressure may become an effective agent of rupture.

AUTHOR.

Swingle, W. W., Remington, J. W., Kleinberg, W., Drill, V. A., and Eversole, W. J.: An Experimental Study of the Tourniquet as a Method for Inducing Circulatory Failure in the Dog. *Am. J. Physiol.* 138: 156, 1942.

The tourniquet method for producing shock, in which both hind legs were constricted by heavy-walled rubber tubing tightly tied around the hips for a period of five hours, has been studied in a large series of dogs.

Of twenty-five untreated control animals, all but one died in shock following the release of the constrictions. The survival periods ranged from three to twenty-seven hours. Associated with the shock condition was a marked swelling of the injured legs, an intense hemoconcentration, and a plasma volume reduction of 49 per cent.

In all animals in which leg infections were prevented by proper antiseptic treatment, the snug bandaging of both legs prior to, or immediately after removal of the constrictions, successfully prevented shock. While shock was prevented by the bandaging, the legs were paralyzed and recovered but slowly.

A plasma transfusion of 25 c.c. per kg. body weight, given immediately after release of the constrictions or later, failed to prevent hemoconcentration, and did not prevent death in nine of twelve dogs.

The same amount of plasma, divided into five doses of 5 c.c. per kg. body weight each, and transfused intermittently over a seven-hour period, prevented shock in all of seven dogs. This positive effect could not be correlated with hemodilution changes.

AUTHORS.

Eyster, J. A. E., and Meek, W. J.: Cardiac Injury Potentials. *Am. J. Physiol.* 138: 166, 1942.

The potential time curve, derived from an injured region of heart muscle by the use of the suction electrode, is remarkably similar in contour and magnitude when recorded from different regions of the same heart, from different animals of the same species, and even from animals widely separated in the animal scale. It represents a local potential change which does not involve the normal muscle contiguous to the injury, although a potential field develops in a conducting field which surrounds it on all sides. The contour and magnitude of the curves differ little in extrasystoles as compared with normal beats, in contrast to the marked differences in unipolar and differential potential time curves in these two circumstances.

The change in an injured region from a negative potential to a positive potential, which occurs when the muscle contiguous to the injury enters into activity, is due to some process in the contiguous uninjured muscle or at the boundary between the injured and uninjured muscle. The start of this potential change at all surface regions of the ventricle precedes the rise of intraventricular pressure by an interval which varies with the location of the injury. At each local region, its onset precedes the onset of local or fractional contraction of the region by an approximately constant interval.

The possible relation of the start of the injury activity potential to the "excitation process" or "impulse" in the contiguous active muscle is discussed.

AUTHOR.

Rosen, S. R., and Smith, K. L.: *The Role of Heart Disease in the Psychoses of the Senium.* *Am. J. M. Sc.* 205: 48, 1943.

The cardiovascular status of forty-three cases of psychoses in the senium was carefully evaluated.

Venous pressure and arm-to-carotid circulation times were determined.

Twelve cases had advanced cardiac disease and showed markedly abnormal values, fifteen cases had minimal organic heart disease without symptomatology; and sixteen had no demonstrable organic heart disease. These last two groups had normal venous pressures and very moderately elevated arm-to-carotid circulation times.

The significance of the above findings is considered, and the role of arteriosclerosis discussed as a possible cause for the moderately elevated circulation time.

It is concluded that cardiac disease plays a minor role, if any, in the psychoses of the senium in which obvious advanced heart disease is not present.

AUTHORS.

Tuttle, W. W., and Templin, J. L.: *A Study of Normal Cardiac Response to Water Below Body Temperature With Special Reference to a Submersion Syndrome.* *J. Lab. & Clin. Med.* 28: 271, 1942.

On the basis of data collected from sixty-eight college women, the following conclusions are drawn concerning the effects of submersion in water:

Submersion in water of swimming pool temperature causes a drop in the heart rate of normally adjusted persons.

The amount of decrease in heart rate due to submersion varies directly with the resting rate.

Failure to experience a decrease in heart rate when submerged in water below body temperature is due to a lack of emotional adjustment (fear) or to a failure to compensate physiologically.

Where emotional factors are controlled, failure to experience a significant drop in pulse rate during submersion in water below body temperature indicates sensitivity to the water.

It is suggested that the conditions causing a failure to make normal adjustments to submersion in water be called the "submersion syndrome."

AUTHORS.

Reingold, I. M., Neuwelt, F., and Necheles, H.: *Circulating Time in the Human Being and in the Dog as Affected by Fasting and by Meals.* *J. Lab. & Clin. Med.* 28: 289, 1942.

The circulating time was determined in a group of human subjects and in dogs. The sodium cyanide method of Loevenhart and associates was employed. During the fasting condition considerable variations of circulating time were found in the human being and in the dog, and following meals the same or somewhat greater variations in circulating time were obtained. The authors' results indicate no significant or uniform changes in circulating time in any one direction in either the fasting or the postprandial state. The nature of the meal did not seem to determine changes in circulating time. The significance of the findings and the discrepancy of the results from those of other workers are discussed.

AUTHORS.

Simonson, E., and Enzer, N.: *Physiology of Muscular Exercise and Fatigue in Disease.* *Medicine* 21: 345, 1942.

The material reviewed shows that there is a quantitative rather than a qualitative difference of physiologic processes in exercise in disease. The limit to which they

can be increased is depressed, and this limit is reached more rapidly in disease. This is due to the fact that many mechanisms involved in muscular exercise become compensatory during rest in pathologic conditions. Therefore, these mechanisms are no longer available to their full extent to meet the demands of exercise; consequently working capacity is reduced or, what is the same by definition, fatigability is increased. Naturally, the impairment of various functions as well as the involvement of compensatory mechanisms vary in different diseases. The patient, naturally, realizes his diminished working capacity as subjective fatigue. This review attempts to show that fatigue and disease are intimately related. This relationship explains why fatigue is the most common complaint of disease.

AUTHORS.

Scherf, D., and Terranova, R.: *Electrocardiographic Studies of the Displacement of S-T Segment in Experimental Thoracic Contusion*. *Rev. argent. de cardiol.* 9: 157, 1942.

The appearance of a displacement of the S-T segment (high or low take-off) in the electrocardiogram, following blunt trauma to the precordium was studied in twenty-five cats. The displacement was obtained in fifteen animals. It disappeared within ten minutes. It is suggested that it is caused by a direct injury to the superficial layers of the myocardium. A high or low take-off of the S-T segment, appearing later, or persisting longer after the trauma, is probably due to a complication, like a pericarditis.

AUTHORS.

Luisada, A.: *On the Value of Mechanical and Acoustic Registration in the Diagnosis of Bundle Branch Block*. *Rev. argent. de cardiol.* 9: 169, 1942.

A clinical case is described in which mitral insufficiency due to rheumatic endocarditis and fibrosis of the myocardium are present.

The electrocardiogram of the patient indicated a right bundle branch block. On the contrary, the acoustic and mechanical records, as well as the fluoroscopy, gave evidence of the delayed contraction of the left ventricle.

A third heart sound was present during the descending branch of the V wave of the venous tracing. A discussion on the possibilities of extra sounds occurring in patients with bundle branch block led to the conclusion that it was impossible to ascertain whether or not it was an opening snap of the mitral valve. The diagnosis of mitral stenosis was, therefore, not supported by the records.

A wide bilateral lesion of the bundle branches should be admitted. In spite of the predominance of the lesion on the left side, the hypertrophy of the right ventricle due to the mitral defect gives to the electrocardiogram the "right-side" type.

The author wishes to call special attention to the importance of the mechanical and acoustic records in order to determine the particular side of a bundle branch block. The electrocardiogram should only point out the existence of widespread lesions below the His bundle.

A dissociation in the C wave of the venous tracing illustrates the existence of two components of it, each related to the activity of one ventricle.

AUTHOR.

Wilburne, M., and Langendorf, R.: *The Significance of the Electrocardiogram With Prominent S Waves in Leads I, II, and III*. *J. Lab. & Clin. Med.* 28: 303, 1943.

Electrocardiograms exhibiting prominent S waves (final inverted phase of the QRS complex measuring 25 per cent or more of the upright phase) in Leads I, II, and III were present in 84 cases of 1,850 consecutive electrocardiograms reviewed.

In 41 of these cases definite electrocardiographic abnormalities, such as left ventricular preponderance, right ventricular preponderance, combined right and left ventricular strain, myocardial infarction, and nonspecific abnormal patterns were found. In 8 others, questionable abnormalities were present.

In 35 cases no other deviations from the normal pattern were observed and these were regarded as the otherwise normal S type of electrocardiogram. The criteria employed in this deduction are described. In 19 of these cases no demonstrable heart disease was present; in 3 the clinical findings were inconclusive; and in 13 there was clinical evidence of heart disease.

It is concluded that electrocardiograms exhibiting prominent S waves in Leads I, II, and III are more common in patients with evidence of heart disease than in normal persons in the population of an electrocardiographic laboratory. However, in an otherwise normal electrocardiogram the S type may be a normal variant, but before this decision is made the case should be thoroughly investigated.

AUTHORS.

Currie, G. M.: Transient Inverted T Waves After Paroxysmal Tachycardia. *Brit. Heart J.* 4: 149, 1942.

A case of recurrent paroxysmal tachycardia in a girl with neurocirculatory asthenia is described; at the time of first observation she was 13 years of age and is now 16; serial cardiograms during and after each attack showed transient inversion of the T waves and a lowering of the S-T interval in one series; there was a return to normal in each case in a month; the degree of the inversion is probably affected by the duration of the attack. The relative importance of the clinical over the cardiographic findings in giving a prognosis in such cases is stressed, and a possible cause of the inversion is put forward.

AUTHOR.

Cooke, W. T., and White, P. D.: Prognosis in Paroxysmal Tachycardia and Paroxysmal Auricular Fibrillation. *Brit. Heart J.* 4: 153, 1942.

When the cardiovascular system is normal, attacks of paroxysmal tachycardia are uncomfortable, but relatively unimportant incidents.

The probability of any attack ceasing is extremely good, but the occurrence of an attack in a patient seriously ill must be regarded with some apprehension, and the occurrence of heart failure as a result of the attack may lead to the formation of intracardiac thrombi and subsequent emboli.

The occurrence of paroxysmal auricular tachycardia in apparently healthy persons seems to have no effect upon the prospect of their longevity. When occurring late in life, the prognosis, in general, is that of the underlying heart disease, if present.

Paroxysmal auricular fibrillation is probably common. When occurring in patients below the age of 40 years, it may be considered as having no prognostic significance, while in later life the occurrence of fibrillation may, in some cases, be the first sign of serious heart disease.

It is impossible to forecast with any certainty either the frequency or the duration of the attacks of paroxysmal auricular tachycardia and fibrillation.

AUTHORS.

Gilson, A. S., Jr.: The Locus and the Nature of the A-V Pause in the Spread of Cardiac Activation. *Am. J. Physiol.* 138: 113, 1942.

It is concluded that an "excitation time" theory may be used to explain the delay normally occurring in the transmission of the cardiac impulse across the atrio-ventricular junction in the turtle heart. Ventricular excitation normally does not

occur during or because of the arrival and rise of the atrial action potential, but during the period of electrical recovery of the atrium. Long atrioventricular delays may involve serial activation of several elements thus multiplying the single junctional pause found in the normal heart.

AUTHOR.

Hunter, A., and Lipscomb, J. M.: Congenital Pulmonary Atresia With Cerebral Thrombosis and Hemiplegia. *Brit. Heart J.* 4: 124, 1942.

Cerebral manifestations in pulmonary atresia and stenosis are well recognized. They have been attributed either to paradoxical embolism, or to cerebral thrombosis associated with the polycythemia. Hemiplegia and epileptiform attacks are recorded by the authors, which were shown at necropsy to be due to cerebral thrombosis. Their transient nature may be explained by the absence of softening of the brain although there was such extreme distension and thrombosis of the cerebral veins.

AUTHORS.

Bremer, J. L.: Transposition of the Aorta and the Pulmonary Artery: An Embryologic Study of Its Cause. *Arch. Path.* 34: 1016, 1942.

Transposition of the aorta and the pulmonary artery is the common factor in many anomalies of the heart, and as such should be the result of some slight and easily produced variation from the normal course of development. Models and drawings of human hearts of 5 mm. and less show great differences in shape, especially of the bulbar region. The lower part of the bulb is transformed into the right ventricle by the outgrowth of sinusoids, sprouting earliest and most profusely from the convex surface of some acute curve. The sharpest curve in the normal bulb points downward and forward, and the spongy substance of the right ventricle, therefore, is chiefly on the ventral and apical walls. In a few of the younger hearts shown, the sharpest curve points downward and backward or dorsally, and in one human embryo studied, the sinusoids, which are just developing, are found on the apical and dorsal walls of the ventricle. Continued growth in this dorsal position would meet the opposition of the diaphragm, and the right ventricle would be forced ventrally. Since the left wall of the embryonic right ventricle is attached to the interventricular canal, ventral displacement can be accomplished only by a rotary anti-clockwise motion, which when transmitted to the distal bulb would counteract the normal dextral torsion and result in transposition.

The expansion of the dorsal and lateral walls at the expense of the ventral wall might also result in the displacement ventrally of the supraventricular crest, the bulboatrial ledge, and the anterior tricuspid ledge, and in their intensification to form more or less complete septums across the ventricle. The ventral pouch bordered by such septums is not, however, the true right ventricle. Stenosis of the pulmonary artery may depend on the efficiency of such septums. Failure of the ventral sinusoids may cause the malformation or absence of the ventral interventricular septum, resulting in "crossed transposition."

"Overriding of the aorta" is due to arrest of development, as all mammalian embryonic hearts pass through this stage before the final separation of the ventricles by the growth of the membranous portion of the interventricular septum. This condition has no connection with transposition.

The main deductions of this paper rest chiefly on the tenuous basis of conditions found in a single human embryo, and are therefore submitted as a theory rather than as a proved exposition of the cause of the anomaly. Yet they trace the logical, mechanical effects of growth forces on an observed variation from normal, and show how these would result in transposition and its many accompanying changes in the heart.

AUTHOR.

Bayles, T. B.: Rheumatoid Arthritis and Rheumatic Heart Disease in Autopsied Cases. *Am. J. M. Sc.* 205: 42, 1943.

Of twenty-three autopsied cases of rheumatoid arthritis, six were found to have changes in the heart valve leaflets and myocardium similar to those that usually follow rheumatic fever. The histologic lesions of one of these six could possibly be considered active and five were inactive in character. Excluding one patient because of definite rheumatic fever and rheumatic heart disease present in childhood, 22 per cent had rheumatic cardiac lesions. The factors of accentuation on cardiac death, the relatively large group with cardiac changes ante mortem as compared to control groups, and the small number of cases (possibly one) with active rheumatic fever lesions have been pointed out. The rheumatoid arthritides in this apparently selected series have a rather high incidence of cardiac lesions similar to those that follow rheumatoid arthritis. A coincidence, a relationship of rheumatic fever and rheumatoid arthritis, or the possibility that the heart disease is related to rheumatoid arthritis, might be inferred from this data. Since patients with rheumatoid arthritis have to die of some other cause than their disease, it would be safer and probably wiser, as yet, to delay a final conclusion until further studies teach us which one of the above three situations truly obtains. In the clinical treatment of these patients, we have preferred to regard the cardiac changes as a coincidence of rheumatic heart disease and rheumatoid arthritis.

AUTHOR.

Bullrich, R. A.: Mitral Stenosis With Arterial Hypertension. *Rev. argent. de cardiología* 9: 87, 1942.

A review is made of observations reported in the literature of arterial hypertension coexisting with mitral stenosis, and thirteen cases of the same combination observed among one hundred and sixteen patients with mitral stenosis are reported and commented upon. It is the author's opinion that arterial hypertension observed in mitral stenosis has no relation to the valvular disease, and is a consequence of the survival of patients to an age where hypertension appears with equal frequency, and by the same causes, as in the general population. The increased percentage of women is due to the accidents of menopause. Arterial hypertension seems to have no influence on the evolution of cardiac insufficiency in patients with mitral stenosis.

AUTHOR.

Findley, T., Edwards, J. C., Clinton, E., and White, H. L.: Clearance of Diodrast, Phenolsulfonphthalein and Inulin in Hypertension and in Nephritis. *Arch. Int. Med.* 70: 935, 1942.

Values for renal blood flow, glomerular filtration rate and tubular secretion of diodrast are reported on a series of normal subjects and patients with essential hypertension, glomerulonephritis and other types of renal disease.

Plasma clearances of diodrast and inulin, even when interpreted in the light of tubular secretion of diodrast, indicate absence of renal ischemia in a high proportion of subjects with uncomplicated essential hypertension.

Under controlled conditions the ratio between inulin clearance and diodrast clearance can represent the "filtration fraction," but high ratios in subjects with hypertension probably result from diminished diodrast extraction rather than from increased filtration pressure.

AUTHORS.

Dalton, J. W., and Nuzum, F. R.: *Critical Statistical Analysis of Data on Renal Function in Grouped Subjects With Essential Hypertension.* Arch. Int. Med. 70: 948, 1942.

Instead of studying differences between single examples and noting variations between two random single samples, a more sensitive observation is made by comparing the results of renal function tests on patients with essential hypertension as a group, with results of the same tests on normal subjects as a group.

Working even in this manner we find that there is no variation of the renal function from the normal in a patient with essential hypertension because of the age of the patient, or because of the duration of the disease.

There is a retardation of the flow of urine in patients with hypertension having high diastolic pressures.

There is some indication of retardation of urinary flow and compensatory nocturia in hypertensive patients on an alkaline diet.

In general, there is fixation of specific gravity and retardation of phenolsulfonphthalein output in patients with hypertension.

The Vollhard concentration and the phenolsulfonphthalein excretion test themselves are of no use clinically for the differential diagnostic purpose of distinguishing between persons with essential hypertension and normal persons in isolated instances. These studies indicate variation in the physiologic processes of the kidney due to a disease process coexistent with essential hypertension.

AUTHORS.

Dempsey, W. S.: *The Adrenal Cortex in Essential Hypertension.* Arch. Path. 34: 1031, 1942.

In a series of unselected routine autopsies on adult subjects, the adrenal glands were removed, fixed in dilute solution of formaldehyde, carefully dissected free of surrounding fat, and the adrenals from each subject weighed together. Paraffin sections were made from a block, cut transversely through the thickest part of each adrenal, and stained with hematoxylin and eosin.

Cases of essential hypertension and a group of nonhypertensive controls were segregated on the basis of rigid criteria. Other cases were appropriately grouped in separate categories.

The average weight of the adrenal glands in cases of essential hypertension is not significantly higher than that in nonhypertensive control cases.

Nodular or adenomatous hyperplasia of the adrenal cortex is not regularly found in association with essential hypertension, and it occurs with considerable frequency in nonhypertensive cases.

The microscopic appearance of tortuosity of the adrenal cortical cords and abundant deposition of fine lipoid droplets in the cortical cells is not consistently associated with the gross finding of irregularity and nodularity of the adrenal cortex.

AUTHOR.

Rich, A. R.: *Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarthritis Nodosa: Another Case Associated With a Sulfonamide Reaction.* Bull. Johns Hopkins Hosp. 71: 375, 1942.

In a previous paper the writer described a series of cases in which periarthritis nodosa was found at autopsy in patients who had had hypersensitive reactions resulting from foreign serum and sulfonamide therapy, and evidence was presented that periarthritis nodosa can be a manifestation of the anaphylactic type of hypersensitivity. The present report describes an additional case, in which periarthritis nodosa developed following a reaction (fever; conjunctivitis) to sulfathiazole.

This case is of particular interest for the reason that there was an opportunity to examine tissue removed from the patient's scrotum at five months and at one week before the sulfonamide reaction occurred, and nine days following the reaction. Periarthritis nodosa was not present in the specimens of scrotum removed before the reaction occurred. It was present there, and widespread throughout the body, following the reaction.

This case, in conjunction with the series described in the previous paper, is a further indication, derived from clinical and pathologic material, that periarthritis nodosa is a manifestation of anaphylactic type hypersensitivity.

In experiments carried out with Dr. John E. Gregory, to be reported presently, typical visceral periarthritis nodosa has been produced by the intravenous injection of a single, large amount of foreign serum into the normal animal, thus providing the opportunity for a protracted circulation of antigen while hypersensitivity develops.

These observations indicate that the continued administration of a sulfonamide or of foreign serum after symptoms of hypersensitivity have appeared, or the injection of a single large amount of foreign serum, carries the danger of producing vascular damage of the periarthritis nodosa type.

AUTHOR.

Sappington, S. W., and Fisher, H. R.: Arteriosclerosis Obliterans: A Study of the Lesions in Occluding Peripheral Sclerosis, With a Note on Mönckeberg's Sclerosis. Arch. Path. 34: 989, 1942.

Forty-four cases of arteriosclerosis obliterans were studied by completely dissecting out the arterial trees from forty-four amputated gangrenous legs. This paper is a report of the vascular lesions present, together with deductions from the findings.

Gross study showed an extraordinary amount of arterial occlusion, averaging 44 per cent of the entire length of the anterior tibial, posterior tibial and peroneal arteries and indicating the great degree of arterial obstruction preceding gangrene.

Microscopic examination confirmed the gross estimate of arterial blockage. The average number of vessels occluded per case was 2.3. The occluding lesions apparently represented various stages and regressions of organizing obstructive clots. Atheroma was not a major or necessarily a participating feature. Vessels with the highest incidence of atheroma exhibited the lowest percentage of occlusions, while those with the highest incidence of closure presented the least degree of atheromatous involvement. It is suggested that abnormalities of the blood flow may be initiating factors in the formation of occluding clots.

The outstanding lesion of the media, calcification, was demonstrated in 100 per cent of thirty-eight cases roentgenologically and in 98 per cent of forty-four cases microscopically, but bone formation was also found in 70 per cent of the cases and a study of the obvious relationship between these two, leads us to conclude that, contrary to the usual conception, bone formation precedes calcification in the media in arteries of the legs, and probably accounts for the major part of the calcification found there.

AUTHORS.

Krupp, M. A.: Urinary Sediment in Visceral Angiitis (Periarthritis Nodosa, Lupus Erythematosus, Libman-Sacks "Disease"): Quantitative Studies. Arch. Int. Med. 71: 54, 1943.

Twenty-one cases of periarthritis nodosa, lupus erythematosus disseminata, Libman-Sacks "disease" and the syndromes of Friedberg and Gross were studied with particular reference to the clinical manifestations of the renal lesion.

In seven cases no specific changes in urinary sediment were discovered, but in fourteen cases a singular picture of the sediment was observed. The uniqueness of this picture lies in the presence of red blood cells, red cell casts, oval fat bodies, fatty casts, broad casts and abnormal quantities of protein in the same specimen of urine. These elements do not occur together in association with glomerulonephritis or with any other renal lesion with which the author is familiar.

This unusual sediment is of diagnostic value in doubtful cases of the disorders just mentioned.

The term visceral angitis is advanced as a convenient clinical designation for these disorders and is not meant to imply a common etiologic relation.

AUTHOR.

Barman, J. M., Moreira, M. F., and Consolazio, F.: The Effective Stimulus for Increased Pulmonary Ventilation During Muscular Exertion. J. Clin. Investigation 22: 53, 1943.

The increase in pulmonary ventilation has been studied in normal men exercising the limbs, first with normal circulation, and then with the circulation cut off by pressure from inflated cuffs.

Very light exercise (at a rate of 12 kilogrammeters per minute) of the flexors of the hand during total ischemia of the arms, usually resulted in a smaller ventilation than when the arms had normal circulation. Release of the ischemia was followed at once by a marked hyperventilation.

In subjects walking uphill on a treadmill (at a rate of 700 kilogrammeters per minute for a 90-kilo subject), total ischemia of both legs results in a marked diminution of pulmonary ventilation, even though the nervous pathways were intact, and release of the ischemia was followed at once by a marked hyperventilation, much higher than the value prior to ischemia.

These results are interpreted to mean that the chemical stimulus for increased ventilation in exercise of these types is far more important than the reflex.

The discrepancies between the authors' results and Harrison's are perhaps due to the fact that consistent results are found only after the subjects have become well accustomed to the experimental procedures by several repetitions of the experiments, and when exercise of sufficient severity is used so that the changes in ventilation and oxygen consumption are relatively large in magnitude.

AUTHORS.

Sigler, L. H.: Hyperactive Vasodepressor Carotid Sinus Reflex. Arch. Int. Med. 70: 983, 1942.

This paper covers a study of the vasodepressor effect induced by the carotid sinus reflex. Seven hundred patients were tested, most of whom had demonstrable cardiovascular disease. Of these, 447 were males and 253 were females.

The patients were divided into four groups according to the original blood pressure. In Group I were included subjects with normal blood pressure; in Group II, patients with low grade hypertension; in Group III, those with moderate hypertension, and in Group IV those with marked hypertension.

It was found that, roughly, about 88 per cent of the males and 82 per cent of the females showed a drop in pressure. If a drop of less than 10 mm. is excluded as of insufficient significance, the response is reduced to about 78 per cent for males and 71 per cent for females. The response occurred more frequently and in greater degree in the older age groups. Also, the higher the blood pressure the more frequent the response and the greater its degree. A drop was more frequent in the systolic pressure than in the diastolic. A drop in pressure often occurred in patients with-

out cardioinhibition but was more frequent in those who also showed cardioinhibition. In such patients, the frequency and the degree of vasodepression roughly corresponded to those of cardioinhibition.

There was a marked difference in response to stimulation on the two sides in many cases. The amount of stimulation required to produce the maximum response varied from case to case and with the position of the patient.

The findings point to the existence of an inherent instability in the vasomotor system in persons who show a marked vasodepression induced by the carotid sinus reflex, which the test helps to demonstrate. The seat of this instability is either in the medullary synapses or in the vasomotor terminals in the vascular tree. Arteriosclerosis is possibly one of the underlying predisposing causes of such instability, as evidenced by the fact that the reflex is most prevalent under circumstances in which arteriosclerosis is apt to occur, that is, when the patient is a man, is of advanced age, and has a high degree of hypertension.

AUTHOR.

Starr, I., and Jonas, L.: Supernormal Circulation in Resting Subjects (Hyperkinemia) With a Study of the Relation of Kinemic Abnormalities to the Basal Metabolic Rate. Arch. Int. Med. 71: 1, 1943.

In a total experience of about 1,400 estimations of cardiac output, one hundred patients were encountered in whom the resting circulation was above normal, a condition we have called hyperkinemia. These patients were usually underweight, and they tended to have resting pulse rates above normal.

Hyperkinemia was encountered in almost all patients with thyrotoxicosis without cardiac involvement and in most patients with patent ductus arteriosus. It was found often in patients with emaciation and less frequently in those with pulmonary abnormalities, fever, anemia, hypertension and peripheral arteriovenous communications.

In seventeen patients, hyperkinemia was present without any complicating condition having been discovered. These patients with essential hyperkinemia resembled patients with thyrotoxicosis in appearance, but the basal metabolic rate was always normal. The clinical characteristics of this subgroup have been described in detail.

The relation between abnormalities of the circulation and the basal metabolic rate has been studied by statistical methods. In uncomplicated hyperthyroidism and hypothyroidism the relation is almost 1 to 1; i.e., on the average, an abnormal increment or decrement in the basal metabolic rate is accompanied by an equal percentage change in the circulation. In heart disease these two functions are related, but the relationship is more nearly 1 to 0.5. Under such conditions the circulation is less than normal for any given metabolic rate, and the higher the metabolic rate the greater the circulatory deficit.

Other instances of deviation from the normal 1 to 1 relationship between circulation and metabolic rate have been found in cases of emaciation and in some cases of hyperthyroidism after partial thyroidectomy.

AUTHORS.

Leiter, L., Eichelberger, L., and Roma, M.: Studies on Renin: The Duration of the Pressor Effect of Large Doses in Conscious Normal and Renally Abnormal Dogs. Observations on Anesthetized and Uremic Dogs, and the Anaphylactic and Pathological Effects of Pig Renin. J. Clin. Investigation 22: 11, 1943.

Trained, conscious dogs, injected with renin intravenously, in single moderate or large doses, sufficient to elevate the mean femoral blood pressure 50 to 100 mm. Hg, gave similar pressor responses whether their kidneys were normal or experimentally abnormal as the result of partial constriction of arteries or ureters, with or without nephrectomy.

Multiple doses of renin, or continuous injection by pump, produced a pressor plateau in renally normal and abnormal dogs, but the blood pressure returned to the control level within an hour after the injection in all of the normal animals and in most of the dogs with unilateral or less extensive bilateral renal lesions.

Marked prolongation of renin pressor activity was observed chiefly in dogs with bilateral, experimental, renal abnormalities following multiple doses or continuous injection of kidney extract, free from depressor material.

Prolonged duration of renin pressor activity also occurred in anesthetized, renally normal dogs and in the majority of conscious dogs with uncomplicated uremia. Dogs with experimental hypertension and uremia reacted irregularly.

Repeated experiments on the same animal with heterologous renin led to the development of anaphylaxis. Dogs sensitized to pig renin reacted normally to dog renin.

The pathologic lesions of experimental malignant hypertension can be induced or accelerated by the injection of foreign renin, not only in dogs with excessive renal ischemia or necrosis, but in some animals without severe hypertension or uremia.

The prolonged effect of renin in conscious dogs with extensive renal abnormality is regarded as evidence in favor of the renin etiology of experimental renal hypertension, and in support of the view that the ratio of normal to abnormal ("ischemic") renal parenchyma is a determining factor in the dog's response to exogenous, as well as endogenous, renin.

The relation of renin to human "essential" hypertension remains an open question.

AUTHORS.

Book Reviews

VASCULAR SPASM. EXPERIMENTAL STUDIES: By A. J. Nedzel, M.D., Associate Professor of Pathology, University of Illinois. University of Illinois Press, 1943, 151 pages, 161 illustrations, \$2.75.

This monograph is devoted chiefly to the presentation of the thesis that vascular spasm is the initial step in the production of the lesions of such diverse diseases as endocarditis, gastric ulcer, and multiple sclerosis. The evidence marshalled in support of the author's position was obtained from experiments on dogs in which, as the author admits, "highly exaggerated" vascular spasm was produced by repeated injections of large doses of pitressin. One wonders whether an equally good case could be made for injections of preparations that act on the vascular bed in a direction opposite to pitressin. It is now well established that animals which are required to absorb appropriate doses of histamine for weeks develop gastric ulcer in a high percentage of cases.

The author's thesis might have been strengthened by positive evidence from experiments in which epinephrine or some other sympathicomimetic drug was used in more nearly physiologic doses.

The monograph should prove of much value to those who are interested in the pathologic effects of large doses of pitressin, which the author has presented in considerable detail. Many will be especially interested in the summaries of the literature in the various sections of the book. The work is excellently printed and is effectively illustrated.

HIRAM E. ESSEX.

A SHORT HISTORY OF CARDIOLOGY: By James B. Herrick, M.D., Emeritus Professor of Medicine, Rush Medical College, Chicago, Ill. Charles C Thomas, Springfield, Ill., 1942, 258 pages, 49 illustrations, \$3.50.

It has often been said that no one should be allowed to enter medical school until he has read Vallery-Radot's *Life of Pasteur*, or the experimental laboratory until he has read Claude Bernard's *Introduction to the Study of Experimental Medicine*. Likewise, Dr. Herrick's monograph is a prerequisite for anyone who aspires to be a cardiologist. It is more comprehensive than R. O. Moon's *Growth of Our Knowledge of Heart Disease* and Rolleston's delightful Harveian Oration on *Cardio-Vascular Diseases Since Harvey's Discovery*. One is struck by the author's dispassionate treatment of controversial questions and his judicious appraisal of men and their work. Much of the material is not new, of course, but the approach often is, and some neglected aspects of the subject have been given the attention which they deserve. Throughout the book one notes the healthy skepticism about "priority" which is so important for sound historiography. The fact that there is no substitute for experience is reflected on almost every page. One who had not lived a long and observant life and had not himself been intimately in contact with many stirring events of medical history could scarcely have written this book.

HORACE M. KORNIS.

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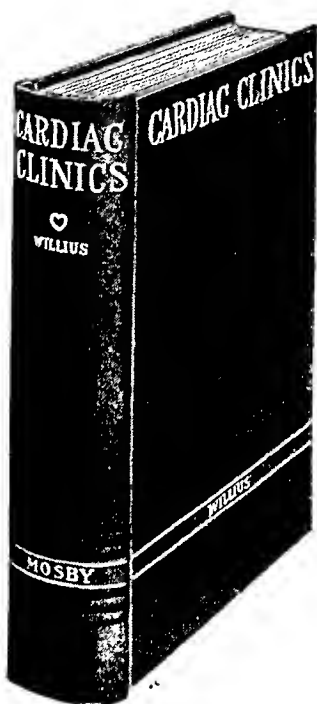
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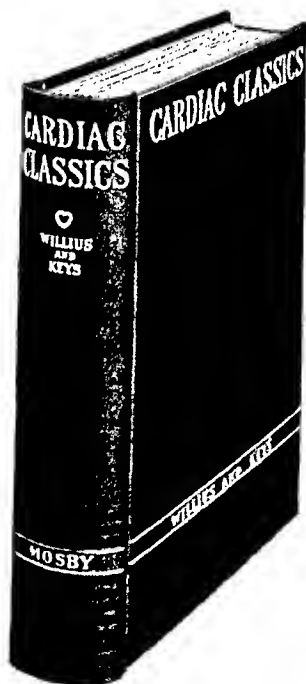
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AUGUST, 1943

No. 2

Original Communications

GLUCOSE DEFICIENCY AS A FACTOR IN THE PRODUCTION OF SYMPTOMS REFERABLE TO THE CARDIOVASCULAR SYSTEM

T. R. HARRISON, M.D., AND ROBERT M. FINKS, M.D.*
WINSTON-SALEM, N. C.

INTRODUCTION

Definition.—The purpose of this communication is to emphasize the relationship of certain disturbances of cardiovascular function to a metabolic disorder characterized by the following features: (1) The symptoms practically always occur two or more hours after meals; (2) they can usually be reproduced by the injection of insulin; (3) they can be relieved by the ingestion of glucose and—in large measure—prevented by dietary regulation; and (4) at the time the symptoms occur the level of the blood sugar is usually either slightly subnormal or within the lower limits of the normal range.

In designating this syndrome, the term “hyperinsulinism” has been avoided because there is evidence that in certain instances other mechanisms than an overproduction of insulin are involved. Moreover, since the values for “blood sugar” (which actually—as measured—represent the total reducing substances rather than the glucose content) are not, in all instances, definitely below the normal range, the phrases “glucose deficiency” and “relative hypoglycemia” are used rather than the unqualified term “hypoglycemia.”

Since 1924, when Harris¹ described spontaneous hypoglycemia and named it hyperinsulinism, numerous publications dealing with this subject have appeared. Most of the authors have been interested in the cases of severe attacks of unconsciousness or convulsions, and relatively little attention has been paid to the milder symptoms. Having been impressed by the frequency of mild forms of relative hypoglycemia, and having observed that the symptoms are often referred to the cardiovascular system, we wish, in this report, to discuss the significance of this

From the Department of Internal Medicine of the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

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*At present Major, M.C., A.U.S.

condition in inducing attacks of a number of well-recognized cardiovascular syndromes.

We have observed thirty-one cases in which relative hypoglycemia appeared to be responsible for disturbances of cardiovascular function. In most of these patients this condition was not the chief disorder, and in several of them it was a purely incidental feature. However, glucose deficiency was frequently an important precipitating factor in various types of cardiovascular attacks, and occasionally it was the sole cause of the symptoms. A summary of the most important features of the thirty-one patients is presented in Table I.

TABLE I
CARDIOVASCULAR SYNDROMES OBSERVED IN THIRTY-ONE PATIENTS WITH
SPONTANEOUS HYPOGLYCEMIA

		NUMBER OF PATIENTS	NERVOUSNESS	FRIGHT	WEAKNESS	PALPITATION	PAIN IN CHEST		DIZZINESS	DYSPNEA (SIGHING)	"CHOKING" FEELING	ARRHYTHMIAS	LOCAL PARESTHESIA	REMARKS
							NON-ANGINAL	ANGINAL						
Entire group		31	25	13	23	17	9	6	9	8	3	7	2	
Group simulating cardiac neurosis*		14	14	9	14	10	8	0	5	8	3	0	0	7 of the patients had both cardiac neurosis and hypoglycemia
Arrhythmias	Premature beats	3	1	1	0	3	0	0	0	0	0	3	0	Hypoglycemia one of several precipitating factors
	Paroxysmal tachycardia	3	3	2	3	3	1	0	0	0	0	3	0	
	Paroxysmal auricular fibrillation	1	1	0	1	1	0	0	0	0	0	1	0	
Angina pectoris		6	3	1	2	0	0	6	0	0	0	0	0	Hypoglycemia a precipitating factor only, in 4 cases. Apparently sole factor in 2 cases
Hypersensitive carotid sinus		2	2	0	2	0	0	0	2	0	0	0	0	Hypoglycemia apparently one of several precipitating factors
Hypertensive encephalopathy		2	1	0	1	0	0	0	2	0	0	0	2	Hypoglycemia apparently the sole precipitating factor in one case; one of several factors in the other case

*Four of these patients had typical menopausal syndromes.

THE DIAGNOSIS OF RELATIVE HYPOGLYCEMIA

The decision as to whether glucose deficiency is a factor in producing symptoms in a given patient should be arrived at through one or more

of the following four different lines of evidence: (1) the history, (2) the glucose tolerance test, (3) the response to insulin, and (4) the effect of dietary treatment.* Each of these diagnostic methods will now be considered in more detail.

1. *The History.*—This is most important because it first suggests the possibility of relative hypoglycemia, and unless taken carefully the condition will usually be overlooked. *Whenever a patient has symptoms referable to the cardiovascular system which recur frequently, but which have never at any time appeared within one hour after an ordinary meal, glucose deficiency should be suspected.* Every patient with recurrent attacks of any kind should be asked the direct question whether the attacks bear any relation to meals. Frequently, the patient, thinking the physician is trying to find out whether the seizures are induced by meals, will answer in the negative. One should then proceed further to ask the patient if he can specifically recall any attack which has occurred shortly after a meal. If the patient is certain that an attack has occurred within one hour after the end of a meal, relative hypoglycemia can probably be excluded, at least as the sole factor, but it cannot be excluded as one of several precipitating factors. If the patient has had numerous seizures and none of these have occurred within two hours after meals it is probable that sugar deficiency may be playing a role.† Some patients have themselves noted that eating tended to relieve their symptoms. However, other patients, because they were afraid to eat during a self-diagnosed "heart attack," do not know whether food affects the symptoms.

2. *Blood Sugar Curves.*—This is a helpful diagnostic procedure but has certain limitations. It should be remembered that one person may have a blood sugar of 40 mg. per 100 c.c. without symptoms, and another person may have definite symptoms of glucose deficiency with a blood sugar of 65 to 70 mg. When one recalls that patients with diabetes may have symptoms from insulin overdosage with a blood sugar at or above the normal value, one realizes that the glucose level is not an absolute diagnostic criterion. Of the thirty-one cases with which this paper deals, and in which the diagnosis of relative hypoglycemia has been made, a glucose tolerance test was carried out in twenty-eight. The patients were given glucose orally—approximately 1 Gm. per kilogram of body weight—and specimens of venous blood were taken at intervals thereafter. Blood sugar was measured according to the Folin-Wu technique. The results may be analyzed as follows:

*A fifth method of study—measurement of the blood sugar level when the symptoms are present—can rarely be carried out because the physician does not usually have the opportunity to see the patient at this time.

†We do not mean to imply that all symptoms which appear more than two hours after meals are of hypoglycemic origin. Such is certainly not the case. There is, for example, no reason to assume that the hunger pain of duodenal ulcer is related to a low blood sugar. Furthermore, we have observed a few instances in which symptoms related to the cardiovascular system appeared quite regularly three to five hours after meals and were relieved by eating, but in which careful studies showed clearly that the seizures were not related to the carbohydrate metabolism. It is probable that, in certain patients with cardiovascular disease, hunger contractions of the stomach may induce symptoms, through reflex effects on the heart or blood vessels.

The *fasting* values for the blood sugar varied between 67 and 121 mg. per 100 c.c.; they were less than 80 in only three instances and more than 100 in only one case. Obviously, measurement of the fasting sugar level is of little or no value in detecting cases in which this disorder is mild.

Wide variations were encountered among the different patients with regard to the highest and lowest values at the various times after the administration of glucose. The lowest blood sugar values were observed at three hours in eighteen instances, at two hours in six cases, and at four hours in four patients. Since in all instances the minimum levels were obtained two to four hours after the administration of glucose, it is evident that insofar as the diagnosis of relative hypoglycemia is concerned, there is no need to take blood samples at one-half, one, and five hours after the sugar has been ingested, although this may be desirable for interpreting the results as regards etiology.

The *lowest* level of blood sugar during the glucose tolerance test varied considerably in different patients. Values of less than 50 mg. per 100 c.c. were observed twice; other minimum levels were: 50 to 59, seven cases; 60 to 69, eleven patients; 70 to 79, seven instances; more than 80, once. No correlation was found between the severity of the symptoms during the spontaneous seizures and the minimum blood sugar value observed in the curves. Thus, one patient became unconscious after a severe attack of pain in the chest, and while in this condition had a blood sugar value of 35 mg. per 100 c.c. He recovered rapidly after the intravenous administration of glucose. However, several days later, when the sugar tolerance curve was measured, the lowest value found was 79 mg. per 100 c.c. of blood. Observations such as this indicate clearly that curves of blood sugar are of limited value in the diagnosis of mild relative hypoglycemia. (Such a statement obviously applies only to sugar curves as usually measured. It is probable that the use of a standard preparatory diet, as recently advocated by Conn,² would have made our data more significant.)

The *shape* of the blood sugar curves was likewise very variable. Four patients showed flat curves, with less than the normal rise and a normal or slightly exaggerated decline. Twelve subjects exhibited a normal rise, followed by an abnormally great diminution. Eight patients displayed an unusually large increase in blood sugar, and in five of these the subsequent decline was striking, whereas in the other three instances the rate of decline was greater than normal but the actual level reached was not less than that of healthy persons. Four patients had curves which seemed to be normal in all respects. Curves of these several types are illustrated in Fig. 1.

The data obtained by measuring the blood sugar of these patients are by no means convincing. Although most of the patients did at times have values somewhat lower than those usually found in healthy persons

of the same age and dietary habits, the differences were not striking. We have frequently observed patients who were entirely free of symptoms at times when their blood sugar values were just as low as the lowest level found in many of these patients. Apparently, different persons display marked variations in their sensitivity to hypoglycemia.

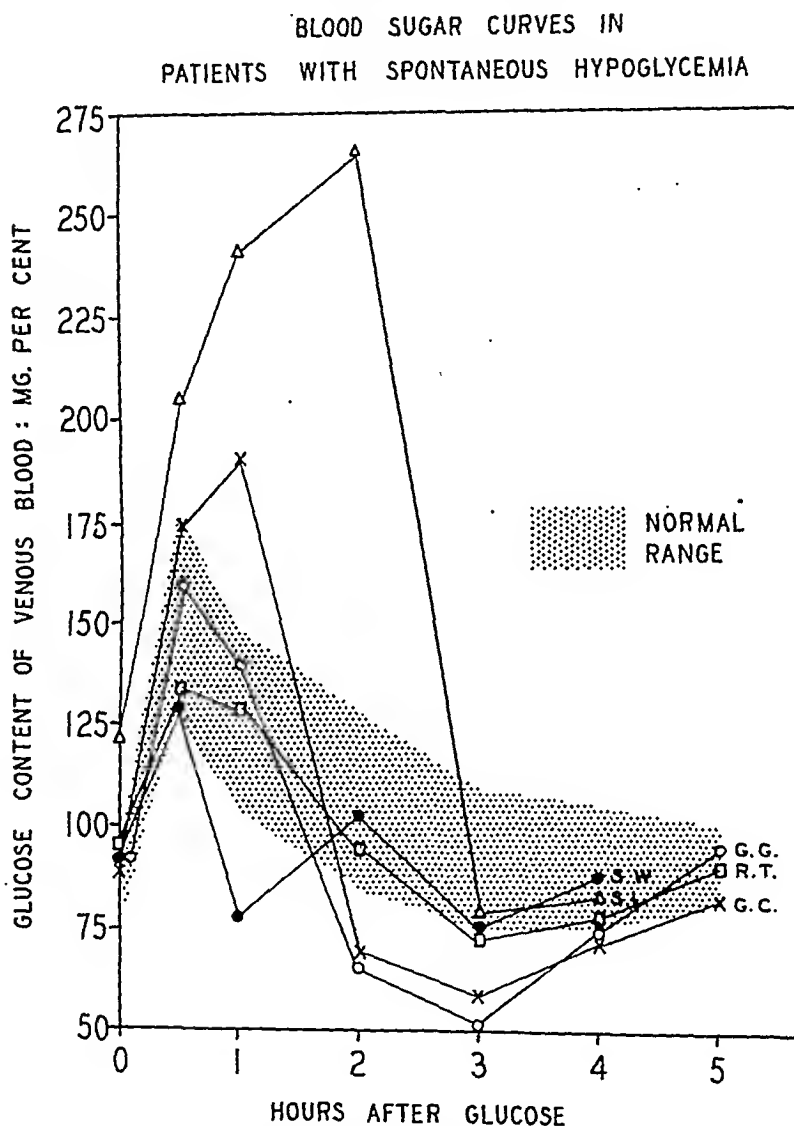


Fig. 1.—Different types of blood sugar curves encountered in patients with symptoms of glucose deficiency are illustrated. At the time the observations were made the patients were free of symptoms. It is probable that the blood sugar curves would have been more significant if the patients had been placed on a standardized diet for several days prior to the studies.

We have gained the impression that the rate of decline in blood sugar may be just as important as the minimal level. Furthermore, it is well known that age and previous dietary habits have a marked influence on the glucose tolerance. Because of these several facts we believe that the measurement of blood sugar often is less useful than other procedures

in determining whether glucose deficiency is a factor in the production of symptoms in a given patient.*

3. *The response to insulin* was not investigated in the earlier cases, but later was studied routinely, and was found to be of considerable value in diagnosis. Ten units of insulin were injected three to four hours after a low-protein meal. If at the end of an hour no symptoms appeared, a second injection of 15 units was given. If after an additional ninety minutes no complaints developed, the patient was usually given his meal and the procedure resumed on the following day, employing larger doses. Since discomfort can be induced in almost anyone by sufficient dosage of insulin, the important point in the test is not whether symptoms occur, but whether the symptoms induced by insulin are the same as those which occur spontaneously. At the beginning of this study it was our custom to take blood for analysis of sugar content at the time symptoms developed. Because of the marked variation in the sensitivity of different persons to hypoglycemia, this procedure has been found to be of relatively little value, and we now rely almost entirely on the patient's statement as regards his subjective sensations. Obviously, care must be exercised in interpreting the subjective reaction of psychoneurotic persons. However, as a rule, the patient's statement about his sensations, and their similarity or dissimilarity to the symptoms which brought him to the physician, proved to be accurate. If there was any doubt the procedure was repeated, using injections of saline or atropine. In this way the factors of malingering and suggestion can be controlled. The insulin response test should not be used on patients who have severe or dangerous manifestations during their seizures. We have used it only rarely on people with angina pectoris or hypertensive encephalopathy.

In interpreting the subjective reactions to the procedure it is important to remember that the induced symptoms may differ from those which occur spontaneously, because fright is likely to be less marked when the symptoms are induced in a hospital or in a physician's office than when they occur spontaneously in a less reassuring environment. Furthermore, a patient may have cardiovascular symptoms of more than one type and due to more than one cause, whereas the administration of insulin induces only those symptoms which are precipitated by glucose deficiency. We have, on several occasions, observed women who had both menopausal and hypoglycemic symptoms. In such instances the patient may state that the "spells" were not reproduced by the injection because she is looking for an attack of "hot flashes," when actually the insulin did reproduce the weakness and palpitation which were among the presenting complaints.

Subject to the qualifications mentioned, the study of the response to insulin has proved to be of considerable value in the diagnosis of

*It is probable that our blood sugar curves would have been more significant if we had adopted a standard preparatory diet, as advocated by Conn.²

glucose deficiency as a factor in causing symptoms. This test has been carried out with negative results on numerous patients who subsequently proved to have no evidence—as ascertained by other procedures—of glucose deficiency. The response to insulin was studied in eighteen of the thirty-one cases included in this report. The test was inconclusive in three cases, but in the remaining fifteen a positive response occurred, i. e., some or all of the symptoms which brought the patient to the physician were reproduced by the administration of insulin. As a rule the patients were quite positive in their statements as to whether the induced symptoms were identical with their spontaneous symptoms, and in most instances further studies showed that their impressions were accurate.

As the result of our experience to date, we are inclined to regard the response to insulin, when properly controlled, as a valuable addition to the glucose tolerance test in the detection of relative hypoglycemia. Both methods, the one subjective and the other objective, have value and limitations.

4. *The Response to Treatment.*—In every case in the series a low-carbohydrate, high-protein diet was prescribed. Since most of the subjects lived in other cities, adequate “follow-up” data are available on only fifteen of the thirty-one patients, and marked improvement has apparently occurred in thirteen of these.* In two instances no benefit was observed from the dietary regime. We suspect that the diagnosis of relative hyperinsulinism was incorrect in these two cases, but, since the suspicion is unproved, they are included in the series. We therefore now regard the response to treatment as one of the most useful means of diagnosis. The reasons why the high-protein diet is employed, and further considerations with regard to the therapy of relative hypoglycemia will be considered later in this communication.

GENERAL CLINICAL PICTURE OF PATIENTS WITH RELATIVE HYPOGLYCEMIA

Most of the studies which have dealt with spontaneous hypoglycemia have been concerned with the severe manifestations. Such patients have usually displayed evidence of gross disturbance of the function of the pancreas (benign or malignant neoplasm, or diffuse hyperplasia), liver, pituitary, adrenals, or kidneys (renal glycosuria). However, the patients dealt with in the present report, which includes much milder instances of glucose deficiency, were quite free of evidence of any gross dysfunction of these organs. Most of them gave a story of utilizing a diet rich in starches, but in some instances no such history could be obtained.

*Obviously, only those symptoms caused by hypoglycemia have been relieved, and in many of the cases these manifestations have been the less important ones. Thus, in cases of angina pectoris the attacks which come on at rest, three to four hours after meals, may be relieved, and the seizures appearing with exertion remain unaffected.

Of the thirty-one patients, twenty were men. The oldest subject was 65 years of age, the youngest, 26 years. Most of the patients were between the ages of 35 and 55 years.

The complaints during the attacks were quite variable; the most common were nervousness (twenty-five patients), weakness (twenty-three instances), palpitation (seventeen cases), and pain in the chest (fifteen cases). In nine cases the pain complained of did not resemble angina pectoris; it consisted of vague preeordial discomfort or aching (six cases), a stabbing sensation (two patients), or a feeling of pressure relieved by belching (one instance). However, there were six patients—discussed in more detail later—who had pain which closely resembled that of angina pectoris. Thirteen of the patients confessed to a considerable degree of fright and anxiety during their attacks, and it is probable that some of the other patients experienced this symptom but were reluctant to admit it. Nine persons mentioned dizziness as a prominent feature of the attacks. Eight subjects complained of dyspnea, which usually consisted of repeated sighing and inability to “get a deep breath,” rather than the panting and labored breathing commonly associated with structural cardiac disease. (Although we have seen four patients with cardiac asthma who obtained marked relief from taking food during the attacks, in none of them could the seizures of dyspnea be induced by insulin.)

Among the less common symptoms were “choking in the throat,” which occurred in three cases and was indistinguishable from the globus hystericus, arrhythmias (seven patients), focal paresthesias (two patients), headache (three patients), “sinking feeling” (three patients), and blurring of vision (two patients). The role of glucose deficiency in precipitating certain arrhythmias, in inducing attacks of hypertensive encephalopathy, and in relation to carotid sinus syncope will be discussed later.

When observed during the attacks the patients usually appear anxious, the heart beat is forceful, and the heart sounds are loud; the pulse volume is full in most instances, but diminished in others. The pulsations of the aorta are usually pronounced in the suprasternal notch, and the peripheral pulsations are prominent. Tachycardia is the rule, but occasionally bradycardia occurs. The blood pressure may vary in either direction, but an increase in pulse pressure is the most common change. The skin is sometimes flushed and sometimes pale. Frequently, the physician does not have the opportunity to observe the patient during the attacks, and, when the examination is made during a period of freedom from complaints, objective abnormalities are usually not found.

The most important *associated disorders* in this series of patients have been as follows: hypertension (nine cases), cardiac neurosis (seven instances), hypothyroidism (six instances), arteriosclerotic heart disease (four patients), menopausal syndrome (four cases), paroxysmal tachy-

eardia (three cases), hypertensive encephalopathy, rheumatic heart disease, and hypersensitive carotid sinus (two cases each), and paroxysmal auricular fibrillation (one case).

RELATIVE HYPOGLYCEMIA IN RELATION TO CARDIAC NEUROSIS

The reader will, no doubt, already have noted the similarity of this clinical picture to that displayed by certain patients with cardiac neurosis. The two conditions may present practically identical features, both subjective and objective. Fourteen of our thirty-one patients were considered at first to be suffering from cardiac neurosis because they presented a multiplicity of complaints associated with a paucity of objective abnormalities. After more careful study we were convinced that seven of these patients were not neurotic at all, for all of their troubles could be accounted for by glucose deficiency. However, the conditions were more complex in the other seven patients of this group. Even after the abnormality in glucose metabolism had been recognized, these patients displayed other features which still warranted the diagnosis of cardiac neurosis. In most of them it was thought that the neurosis had resulted from the mental stress brought about by fear of heart disease because of symptoms which were originally induced by the relative hypoglycemia, but which the patient ascribed to "heart trouble." Even in such cases the correction of the glucose deficiency by proper dietary measures resulted in marked relief of the neurotic symptoms, because one of the chief causes of fear had been removed.

One patient, who was diagnosed as having both relative hypoglycemia and cardiac neurosis, merits especial comment because of certain unusual features. This 49-year-old business man complained of palpitation, weakness, choking in the throat, and fullness in the head. These symptoms appeared only when he became engaged in a business argument. He thought that he had cardiac disease, but had consulted several physicians, all of whom had told him that his heart was normal and that his trouble was due to "nerves." On careful questioning it was found that his important business conferences were commonly held about two or three hours after his breakfast, which consisted almost entirely of carbohydrates. The heart was objectively normal to all of the ordinary methods of examination. The glucose tolerance test (Fig. 1, patient G. C.) displayed a high peak (190 mg. per 100 c.c. at one hour, followed by a sharp decline to 58 mg. at three hours. The injection of insulin—15 units—produced a typical attack. His seizures could be prevented by having his business conference held one hour after a protein-rich breakfast rather than three hours after a high-carbohydrate meal. Marked improvement has persisted for nearly two years since his dietary habits were changed. However, he still has some heart consciousness and is still fearful of heart disease. The observation that in this patient the combination of mental stress and hypoglycemia was apparently necessary in order to produce the complaints suggests that the symptoms may have been related to release of adrenalin. However, this suspicion remains unproved.

Four of the fourteen patients who experienced symptoms resembling those of cardiac neurosis were also suffering from the menopausal syndrome. It was difficult to disentangle the symptoms of the latter condition from those of relative hyperinsulinism, for both conditions

are common causes of palpitation, tachycardia, and other functional disturbances of the circulation. In none of these patients did the injection of insulin induce "hot flashes," and this symptom was not relieved by dietary regulation. In these four patients benefit occurred both from estrogenic therapy and from control of diet. Neither procedure alone was as helpful as the two together. Our data do not justify any conclusions as to the frequency of glucose deficiency as a factor in the production of some of the cardiovascular symptoms commonly observed in women during the menopause.

The similarity between the clinical manifestations associated with a decline in blood sugar and the phenomena of true cardiac neurosis is so great that we are no longer willing to make a dogmatic diagnosis of cardiac neurosis without excluding spontaneous hypoglycemia.

RELATIVE HYPOGLYCEMIA AS A FACTOR IN PRECIPITATING CERTAIN CARDIOVASCULAR SYNDROMES

Many cardiovascular disorders are associated with recurrent attacks of the particular symptom which is troublesome to the patient, and the seizures are usually separated by intervals of comfort. Such attacks are of the most varied types, and, among the factors which may precipitate them, a decline in blood sugar plays an important role. Some of the conditions which can in certain cases be induced by relative glucose deficiency are the following:

1. *Disturbances of Cardiac Rhythm.*—We have seen three patients with paroxysmal auricular tachycardia whose attacks tended to occur two or more hours after meals; regulation of their diet was followed by a diminution in the frequency of the attacks. We do not mean to state that a low blood sugar is a factor in inducing attacks of paroxysmal tachycardia in all patients, or in inducing all of the attacks in any patient. Such is not the case. Several patients with recurrent attacks of paroxysmal tachycardia have been carefully studied for evidence of hypoglycemia with entirely negative results. However, there are certain cases of this disorder in which a low blood sugar may be one of several precipitating factors; the others are abdominal distention, emotional upsets, unusual muscular effort, the ingestion of iced drinks, fatigue, or, in many instances, are unknown.

Paroxysmal auricular fibrillation has not in our experience been commonly associated with a low blood sugar. However, this association seemed to be definite in one instance.

Of the thirty-one patients included in this study, three complained of "skips" of the heart as a troublesome feature of the attacks. In each of these cases ventricular extrasystoles were induced by insulin, and their frequency was much reduced after a high-protein diet had been instituted. Obviously, we do not regard glucose deficiency as the usual cause of premature beats, but in an occasional case the decline in blood sugar seems to be an important exciting factor.

2. *Angina Pectoris*.—The relationship of glucose deficiency to angina pectoris is somewhat complex, and will be discussed in more detail later. Here we shall be satisfied with pointing out that attacks of angina pectoris which occur at rest, with no apparent cause, are sometimes due to spontaneous hypoglycemia. Such seemed to be the case in six patients in this series.

3. *Hypertensive Encephalopathy*.—In two instances the relationship between recurrent attacks of hypertensive encephalopathy and relative glucose deficiency seems to have been established. We suspect that such a relationship existed in two other patients, but their condition was so serious that investigation of the response to insulin seemed unjustifiable. Since treatment by diet caused the attacks to become less frequent but did not result in their complete cessation, it seems clear that relative hypoglycemia was only one of several precipitating factors in these cases, and, in our experience, it plays no role at all in the majority of cases of hypertensive encephalopathy.

4. *Hypersensitivity of the Carotid Sinus*.—Two patients were observed who had spontaneous attacks of syncope; their seizures could be readily reproduced by pressure on the carotid sinus, but only provided such pressure was applied three to four hours after meals. Apparently, the sensitivity to stimulation of the carotid sinus may, in certain cases, be increased by relative glucose deficiency.

5. *Paroxysmal Dyspnea*.—Four patients were observed with left ventricular failure and paroxysmal attacks of shortness of breath; they said that the attacks appeared only on an empty stomach and were relieved by eating. One of these patients was not studied carefully, and the relationship of his attacks to hypoglycemia remains uncertain. The other three patients were thoroughly investigated, and, even though the relief of dyspnea by taking a small amount of food was striking, it was found that the attacks bore no relation to a low blood sugar. The blood sugar during the attacks was normal. The administration of insulin induced weakness, sweating, and palpitation, but no dyspnea. Furthermore, it was found that when the attacks began, relief would come within one minute after the ingestion of food, or even after a cup of coffee only. Two of these patients were given trials with high-protein diets but obtained no benefit. Apparently in these cases some reflex factor, possibly hunger contractions from the stomach, was responsible for the relationship of the attacks to lack of food. (It is possible that patients of this type are fairly common, and that some of the cases in the literature of supposed "hyperinsulinism" represent various reflex disturbances. Furthermore, we have seen one patient who had symptoms suggestive of hypoglycemia, but who appeared on further study to have reflex cardiac acceleration as the result of the pain of duodenal ulcer.)

These four patients with cardiac asthma are, of course, not included in the series because their symptoms were not caused by a decline in

blood sugar. However, there were eight patients with hypoglycemia who had the sighing breathing, associated with a feeling of inability to take in enough air, which is so commonly seen in neurotic subjects. Furthermore, we have recently observed a patient who had typical hysterical hyperpnea which resulted in tetany; her hyperpnea occurred only when she became frightened as the result of palpitation and premature beats induced by glucose deficiency.

THE RELATIONSHIP OF RELATIVE HYPERINSULINISM TO ANGINA PECTORIS

It is not uncommon for patients who have typical angina of effort, not related to the blood sugar level, to have occasional attacks of discomfort at rest and without obvious cause. That such attacks may be induced by an unusually large meal, by emotion, or by temporary disturbances of the cardiac rhythm is well known. It is also known that hypoglycemia induced by insulin may cause anginal attacks in diabetic patients with coronary disease. However, Sippe and Bostock³ have pointed out that *spontaneous* hypoglycemia may precipitate attacks of angina pectoris, and in our experience this is one of the most important causes of mild anginal attacks at rest, in the absence of an obvious precipitating factor. Whenever a patient has unexplained attacks of angina pectoris at rest, relative hypoglycemia should be suspected, and, if found, appropriate treatment instituted.

Spontaneous hypoglycemia and angina pectoris may be related in another way, i. e., the lowering of the blood sugar may induce an attack of paroxysmal tachycardia or of paroxysmal auricular fibrillation which in turn may lead to an attack of angina pectoris.

In the instances which have been mentioned, there already is some cardiac disturbance which can be precipitated by a low blood sugar. However, in rare instances, typical attacks of angina pectoris may occur as the result of hypoglycemia in patients who have no other demonstrable cardiac abnormality. This remarkable sequence of events was observed in a 27-year-old white woman who complained of recurrent attacks of constrictive pain radiating from the substernal and precordial region to the left shoulder, the left arm, and the ring and little fingers of the left hand. The attacks were not caused by muscular effort, and she was able to engage in athletics without symptoms. Although she had had numerous seizures, she could not recall any which had appeared within ninety minutes after a meal. The heart was entirely negative to physical examination, and no abnormalities were revealed by either electrocardiographic or fluoroscopic methods. Her glucose tolerance curve was abnormally "flat" (patient S. W., Fig. 1). The attacks could be induced by insulin, and the pain was relieved by either nitroglycerin or orange juice. During such an attack, elevation of the S-T segments in the electrocardiogram was noted. The use of a high-protein, low-carbohydrate diet, with intermediate feedings, was followed by marked relief.

The occurrence of anginal attacks without relation to effort in this case might be cited as evidence against the idea, first expressed by Keefer and Resnik,⁴ and now widely accepted, that angina pectoris is dependent on myocardial anoxia. However, since insulin causes an increase in the cardiac output,⁵ and hence in the cardiac work, and,

further, since one would expect deficiency of fuel to have the same general effect as deficiency of oxygen, the occurrence of angina during glucose deficiency in a patient with no structural lesion capable of producing anoxia cannot be considered as evidence against this well-established concept.

THE RELATION OF THE SYMPTOMS OF GLUCOSE DEFICIENCY TO THE APPARENT BLOOD SUGAR LEVEL

Although the idea that a direct quantitative relationship exists between the severity of the symptoms of glucose deficiency and the level of the blood sugar, as ordinarily measured, seems to be widely accepted, there is convincing evidence that such is not the case. It should be remembered that the usual methods for estimating blood sugar are not specific, but measure instead a number of substances which reduce copper sulphate. Patients with diabetes may have symptoms of hypoglycemia with apparent values for blood sugar which are well within the normal range. Likewise, a patient may be without symptoms when the blood sugar is markedly reduced, and, at other times, have severe hypoglycemic reactions with similar sugar levels. Such an instance has recently been reported by Conn and Conn.⁶

In order to obtain further data on this question, we have made a number of observations on persons with symptoms of glucose deficiency, either spontaneous, or induced by insulin. The following protocols are illustrative.

Subject M. T., a woman, 42 years old, frequently had weakness, dizziness, blurring of vision, and palpitation three hours after meals which were relieved by eating. The blood sugar one hour after a light carbohydrate meal was 159 mg. per 100 c.c. Two hours later, when the typical symptoms appeared, her blood sugar was 80. The ingestion of 25 Gm. of glucose produced relief in ten minutes, and raised the blood sugar to 100. These observations were repeated on two other occasions, and values of 64 and 73 were found during the symptoms. On another date she was given 20 units of insulin, and the symptoms were marked when her blood sugar reached 56. It subsequently fell to 27, with no increase in symptoms except for the appearance of sweating and hunger. Twenty minutes after eating a bar of candy the blood sugar was 50, but all symptoms were relieved.

Subject M. M., a 38-year-old man, had mild attacks of palpitation, sweating, and weakness two to four hours after carbohydrate-rich meals which were relieved by eating. During such an attack his blood sugar was 62. He was given 20 units of insulin and his symptoms became intensified; the blood sugar was 38. Within a few minutes after the ingestion of 25 Gm. of glucose he was relieved, but the blood sugar was 41.

Subject T. H., a man, aged 41 years, had no manifestations of spontaneous hypoglycemia. Three hours after a meal his blood sugar was 82. Forty-five minutes after receiving 20 units of insulin his blood sugar was 26. He had no symptoms other than slight dizziness and a feeling of warmth in the abdomen. Twenty minutes later he had blurring of vision, marked hunger, and profuse sweating, and the blood sugar was 32. Fifteen minutes after eating two candy bars his blood sugar was 47 and the symptoms had disappeared.

These observations indicate that: (1) Certain persons may have symptoms of glucose deficiency when the blood sugar is normal. (2) Other persons may have extremely low values for blood sugar with minimal symptoms. (3) Relief of symptoms may occur with only a slight increase in blood sugar. (4) In a given patient there is very little parallelism between the level of blood sugar and the severity of symptoms. (5) Symptoms of glucose deficiency are more likely to be related to the rate of decline than to the absolute level of blood sugar. (6) Glucose deficiency, when induced by insulin, is likely to be associated with lower levels of blood sugar than when it occurs spontaneously.

THE MANAGEMENT OF RELATIVE HYPOGLYCEMIA

Of the several different plans we have tried in various cases, the most generally satisfactory has been the low-carbohydrate, high-protein diet suggested by Conn, et al.⁷ The three regular meals are relatively small, and are supplemented by intermediate feedings; the total caloric intake is sufficient to maintain the weight of thin patients, or can be adjusted to cause a slow loss of weight in obese patients. High-carbohydrate diets with frequent feedings have not usually caused improvement. Apparently the marked rise in blood sugar produced by such feedings leads to excessive insulin production. Diets low in carbohydrate and abundant in fat have been beneficial, but apparently less so than the high-protein diet. Newburgh and Conn showed that, after a protein meal, the blood sugar curve is relatively stable, and free of the postprandial decline which commonly occurs after a carbohydrate meal; this is because the protein is converted into amino acids which, in turn, are changed into glucose.

DISCUSSION

Although relatively little has been written about *spontaneous* hypoglycemia in relation to the vascular system, a few isolated reports have appeared. Most of these have been summarized by Harris,⁸ who cites tachycardia, bradycardia, palpitation, extrasystoles, sense of suffocation, and precordial pain as some of the manifestations which may occur. Waters⁹ reported a patient with paroxysmal tachycardia whose attacks were precipitated by glucose deficiency. Sippe and Bostock³ emphasized the importance of spontaneous hypoglycemia in the production of angina pectoris.

The circulatory manifestations of *induced* hypoglycemia have been studied by a number of authors. The prominent arterial pulsations mentioned by Wiechmann and Koeh¹⁰ and Messinger¹¹ appear to be related to the increase in cardiac output which was demonstrated by Lauter and Baumann,¹² and by Ernstene and Altshule.⁵ Messinger,¹¹ studying patients with schizophrenia who were treated by insulin shock, mentions flushing, pallor, increased pulse pressure, bounding pulse,

"pistol-shot" sounds over the arteries, capillary pulsations, and even transitory to-and-fro murmurs along the left sternal border. With the exception of the diastolic murmur, these phenomena are those which we have commonly observed in our patients with glucose deficiency. The signs, in general, are similar to those seen in patients with thyrotoxicosis or, for that matter, in normal persons immediately after exercise. These typical manifestations of the overactive heart are, as has been pointed out elsewhere,¹³ the usual signs of an increase in cardiac output. During hypoglycemic states there are at least two factors which may cause an increase in cardiac output. One of these is the release of epinephrine, and the other is an effect similar to that of anoxia, for it seems obvious that fuel deficiency will tend to produce in the tissues metabolic disturbances similar to those induced by oxygen deficiency. Whether the circulatory manifestations of hypoglycemia are entirely the result of epinephrine release, are dependent on dilatation of peripheral blood vessels as the result of fuel deficiency, or are related to other and unknown factors is uncertain. Since both anoxia and epinephrine cause similar clinical evidences of circulatory overactivity, and since both cause an increase in cardiac output,^{14, 15} it is probable that each mechanism may play a role in producing the hemodynamic changes accompanying hypoglycemia.

Throughout this communication we have used the terms "relative hypoglycemia" and "glucose deficiency" to designate, respectively, the syndrome and the metabolic disorder under discussion. These terms are not beyond criticism. The fact that administration of sugar relieves certain symptoms does not prove beyond question that lack of sugar is the essential factor in their production. It is possible that, in certain patients, and especially those who have symptoms with apparently normal values for blood sugar, the primary disturbance may be in some of the enzymes or hormones which are concerned in the complex processes of transfer, storage, release, and combustion of carbohydrate. The balance of these factors may be so disturbed that in certain persons a normal carbohydrate metabolism can be maintained only in the presence of a high "sugar pressure" in the tissue fluids. Until more is known concerning the disorders of the intimate processes of glucose metabolism it seems justifiable to use the term "relative hypoglycemia," even though it is recognized that the glucose deficiency is a result, and not a cause, of the unknown primary disorder. Meanwhile, the realization that measurements of blood sugar have only limited value in the detection of these common and mild disorders of carbohydrate metabolism should lead to the more widespread use of the diagnostic methods which have been discussed. The recognition of these disorders is particularly important because they commonly produce anxiety, through fear of heart disease, out of all proportion to the discomfort, and because they can usually be satisfactorily treated by regulation of the diet.

SUMMARY

Disturbed carbohydrate metabolism may precipitate various manifestations referable to the cardiovascular system. These manifestations can be recognized by their appearance two or more hours after meals, their relief by the ingestion of glucose, and their reproducibility by administering insulin. When the symptoms are present, the blood sugar level is usually within the lower limits of normal, or only slightly subnormal. The disturbance of carbohydrate metabolism which is responsible for these symptoms has, for want of a better term, been designated as "relative hypoglycemia."

Relative hypoglycemia is a common factor in the production of symptoms referable to the circulatory system; and has been found in thirty-one of the last two hundred four of our patients with cardiovascular complaints.

Relative hypoglycemia may produce subjective and objective manifestations identical with those commonly observed in patients with cardiac neurosis. The two conditions can be differentiated only after the most thorough study, and they frequently coexist.

Relative hypoglycemia may be a "trigger" factor in precipitating various arrhythmias (including paroxysmal tachycardia), as well as attacks of angina pectoris, hypertensive encephalopathy, carotid sinus syncope, and circulatory disturbances associated with the menopause.

Relative hypoglycemia frequently is associated with pain in the chest which is nonanginal in character. Occasionally it induces, in patients with typical effort angina, attacks of angina pectoris at rest. Rarely patients without any evidence of structural cardiac disease may have, as the result of glucose deficiency, attacks of severe pain which are identical with seizures of angina pectoris in all respects except for the absence of a relation to muscular effort.

The circulatory manifestations of relative hypoglycemia are the same as those observed after the experimental or therapeutic administration of insulin. They appear to be related to two mechanisms: release of epinephrine, and alterations comparable to those which occur in anoxia. The increased venous return, so brought about, causes an augmented cardiac output and the typical signs of the "overactive heart."

The diagnosis of the milder instances of relative hypoglycemia has been discussed, and it is concluded that the attempt to reproduce the symptoms in a given case by insulin administration is, in certain patients, a more valuable method than the glucose tolerance test. Both methods are less important than the history.

When relative hypoglycemia is causing symptoms, marked benefit can usually be obtained by the use of a diet which is poor in carbohydrates and rich in protein, with intermediate feedings. Observation of the response to such a diet is therefore at times a helpful diagnostic measure.

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THE EFFECT ON MAN OF POTASSIUM ADMINISTRATION IN RELATION TO DIGITALIS GLYCOSIDES, WITH SPECIAL REFERENCE TO BLOOD SERUM POTASSIUM, THE ELECTROCARDIOGRAM, AND ECTOPIC BEATS

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SAMPSON and Anderson,¹ in 1930 and 1932,² demonstrated that approximately 50 per cent of ectopic heart beats in persons with otherwise normal hearts or with various types of heart disease could be abolished by the oral administration of different potassium salts in doses varying from 1 to 15 Gm. In this series there was one patient who had auricular fibrillation and bigeminy; the ventricular ectopic beats were produced by digitalis intoxication. These ectopic beats disappeared after the administration of 3 Gm. of potassium chloride.

It was believed that the changes in the physicochemical state of the heart muscle which tend to produce ectopic beats probably have different origins, for the ectopic beats were abolished in only 50 per cent of the cases in which potassium was used.

In view of the work that has been done on the effect of digitalis on blood serum potassium and the potassium content of heart muscle, the single case of digitalis intoxication in this series suggested that there may be a correlation between the disturbing effect of digitalis on the potassium balance of the heart muscle and its counteraction by potassium administration. If this effect of digitalis were a constant cause of ectopic beats, potassium administration should uniformly abolish them. It was therefore considered important to make a further study of digitalis therapy and digitalis intoxication in the light of the possible effects of potassium administration on the potassium content of the blood serum and on ectopic beats.

The theory that an alteration of the calcium-potassium ratio in the heart muscle in favor of calcium can explain the action of digitalis has been advanced by several investigators, notably Cattell and Goodell.³ The experimental observations in support of this theory are (1) that an excess of calcium increases the force of myocardial contraction, and potassium tends to relax the myocardium;⁴⁻⁸ (2) that the addition of calcium increases the tendency toward ectopic beat formation,⁹ whereas potassium generally diminishes it;^{3, 10-13} and (3) that the T waves of the electrocardiogram tend to be elevated by potassium^{3, 14-16} and depressed by calcium.²¹⁻²⁴ (The T waves may be either elevated or de-

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pressed by potassium, as shown in cats by Chamberlain, et al.,¹⁷ and in man by Bamber¹⁹ and Stewart and Smith.²⁰)

Likewise it has been demonstrated (1) that digitalis is ineffective unless at least a small amount of calcium is present in the perfusate of heart muscle;^{25, 26} (2) that serious and occasionally fatal synergism occurs when calcium salts are injected into patients under digitalis therapy,^{27, 28} although Winkler, et al.,¹⁶ could not demonstrate synergistic effects of digitalis and calcium in dogs; (3) that digitalis and strophanthin cause loss of potassium from the heart muscle;^{4, 30-32} and (4) that strophanthin sensitizes the heart to acetylcholine and to high vagal tone,^{33, 34} which two factors, in turn, are reported to be associated with potassium accumulation in muscle tissue and probably to potassium release from muscle cells.³⁵

Although these data seem to support the "calcium" theory of digitalis action, contradictory evidence has been assembled. Wedd,³⁷ Hagen,³⁸ and Boyer and Poindexter³⁹ demonstrated an increase in the potassium content of the myocardium when digitalis glycosides were used in therapeutic doses. These observations were adapted by the latter investigators to the conception that the functional integrity of the muscle cell is partially dependent on its potassium content, and that digitalis partially prevents the loss of potassium from the myocardium when the heart is hypertrophied or damaged (Harrison, et al.,⁴⁰ Calhoun, et al.,⁴¹ Wilkins and Cullen,⁴² Mangum, Reichle, and Myers^{43, 44}). A parallel has likewise been drawn between the lessening in the muscular weakness in Addison's disease after the deposition of potassium in muscle as a result of adrenal cortical hormone therapy, and this action of digitalis. It is of interest that there is a close chemical relation between desoxycorticosterone and digitoxigenin. The return of muscular power with the administration of potassium to patients with familial periodic paralysis (Stewart, et al.⁴⁵) and Simmonds' Disease (Anderson⁴⁶) also indicates the importance of proper potassium concentration in the maintenance of normal muscular function. In these diseases the T waves become elevated, indicating a cardiac, as well as a somatic, muscular effect. Thyrotoxicosis⁴⁷ also produces a loss of potassium from the muscle cell which is partially prevented by adrenal cortical hormone therapy.⁴⁸ This may explain the increased dosage of digitalis necessary to affect a thyrotoxic patient with heart failure. The reverse of this action may hold true in myxedema.

In contrast to the disagreement on the effect of digitalis glycosides in therapeutic doses is the consensus of investigators that toxic doses of these substances uniformly cause a loss of potassium from somatic and cardiac muscle.^{30, 37, 38} It would be expected that, if improvement in cases of myocardial inefficiency is dependent on retention of potassium

*Current knowledge concerning potassium concentration in intracellular interstitial fluids and plasma in adrenal cortical insufficiency is not, we believe, in conflict with this work. An excellent summary of this subject is given by Kepler, E. J., and Wilson, D. M.: Diseases of the Adrenal Glands; Addison's Disease, Arch. Int. Med. 68: 979, 1941.

brought about by moderate doses of digitalis, toxic doses of digitalis, by causing potassium loss, would reduce the efficiency of the heart, but this is not the common clinical experience in cases in which moderate digitalis intoxication is indicated by nausea, visual symptoms, and ectopic heart beats.⁴⁰ It must, however, be recognized that digitalis in therapeutic doses occasionally abolishes ectopic beats, and produces them in toxic doses. One might assume that this is due to the effect on the potassium content of the heart muscle, but even this assumption cannot be accepted in the light of the action of oral doses of potassium in a test case (Case 13). In this case ectopic beats were present before digitalis was administered, and they were not affected by potassium. They did, however, disappear when digitalis was given in therapeutic doses. When ectopic beats reappeared with digitalis intoxication, they were promptly abolished by a 5 Gm., oral dose of potassium. This case presents not only significant evidence that there are physiochemical differences in the origin of ectopic beats, but also that there is a specific relation of these beats to the change of the potassium content, or the potassium-calcium ration of the heart muscle, as affected specifically by potassium administration and digitalis therapy.

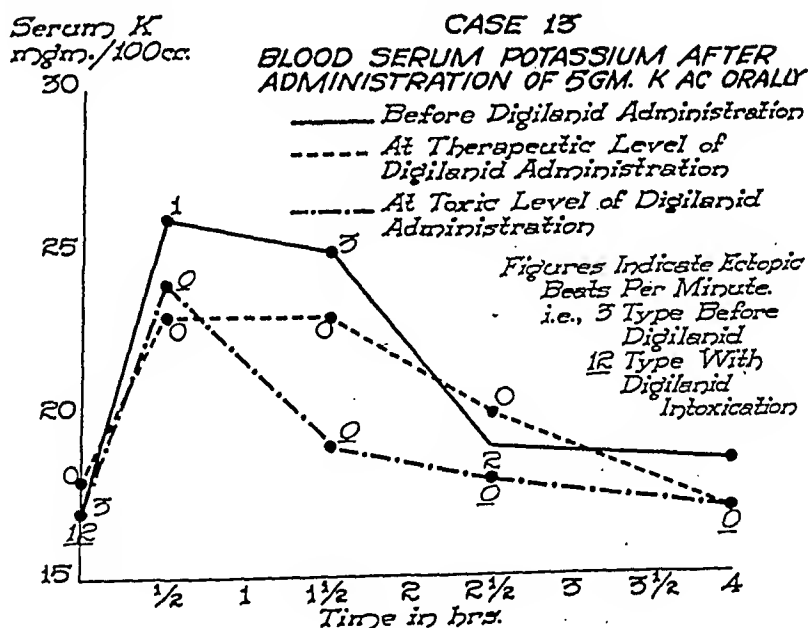


Fig. 1.

Since neither theory entirely fits the facts, no true explanation exists for the digitalis action on the calcium-potassium balance or for functional integrity of the myocardium. Simultaneous studies of the calcium as well as the potassium content of the heart muscle during digitalis therapy may uncover the determining factors.

The work presented in this paper is concerned largely with toxic doses of digitalis glycosides, and therefore only secondarily with the therapeutic effect of digitalis on the potassium or calcium-potassium balance in the myocardium. Thirty-three patients were studied; thirty-one, who

were more than 60 years of age, had arteriosclerosis, and two, aged 45 and 62 years respectively, had rheumatic heart disease. The pure lanatosides A, B, and C of digilanid were used chiefly in order to be sure of consistency and uniformity of action and that the doses administered were comparable in milligrams of active substance.⁵⁰ Digitalis leaf tablets were used orally in two instances, Cedilanid in one instance, and Digilanid (Sandoz), either initially or for at least two weeks after discontinuance of digitalis, in twenty-eight instances. All of this group were given large enough doses, as indicated in Table I, to produce constant nausea and marked slowing of the ventricular rate when auricular fibrillation was present. Thirteen, or slightly over one-third of these patients, developed ventricular ectopic beats. Whether this low incidence of ectopic beats was due to the particular lanatosides used or to failure of criteria of intoxication cannot be stated. The latter seems improbable because of the other evidences of toxicity.

In seventeen cases, studies were made of the blood serum potassium by the argenti-cobalt-nitrate method,⁵¹ with final readings on the Evelyn colorimeter.⁵² Table I illustrates eighteen cases in which potassium was given. In one of these, blood potassium studies were not done (Case 6). In most instances these were made when the patient was fasting, and at one-half hour, one and one-half hours, two and one-half hours, and four hours after the administration of 5 Gm. of potassium acetate orally in a 25 per cent aqueous solution. In three instances, 10 Gm. of potassium acetate were used. In three cases (Cases 9, 10, and 16) preliminary studies were made, but inasmuch as no ectopic beats were produced by toxic doses of digitalis, no potassium estimations were made after digitalis had been given.

Blood serum potassium estimations have been made by other investigators after the administration of potassium salts orally to human subjects.^{3, 10, 14, 15, 53-55}

The curves obtained on our patients resemble those reported previously, except that the maximum rise of the potassium level occurred later in the previously reported cases. There was some variation in the time of the maximum rise of the blood serum potassium which was probably the result of differences in absorption. This maximum was reached in one-half hour in nine cases, and in one and one-half hours in five cases. In general, the potassium content of the blood serum was nearly identical one-half and one and one-half hours after potassium administration, and it fell practically to the fasting level within two and one-half to four hours. In one case (Case 12), the potassium content of the specimens at the one and one-half hour period was higher than at the one-half hour period, and, after digitalis therapy, the higher level was at the one-half hour period in one instance, and the levels were identical in one other instance.

As is best illustrated by Case 14, there was no essential difference in the blood serum potassium curve before digitalis was given and at the

later dates, when the patient had received digitalis in therapeutic or toxic doses.

Castleden¹⁰ showed that ectopic beats could be abolished by the oral use of potassium after they had been produced by epinephrine and

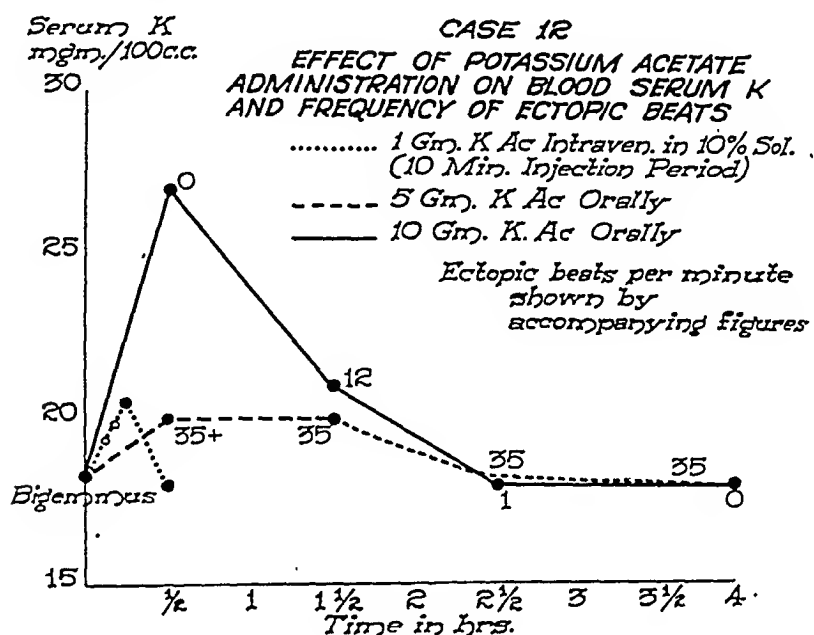


Fig. 2.

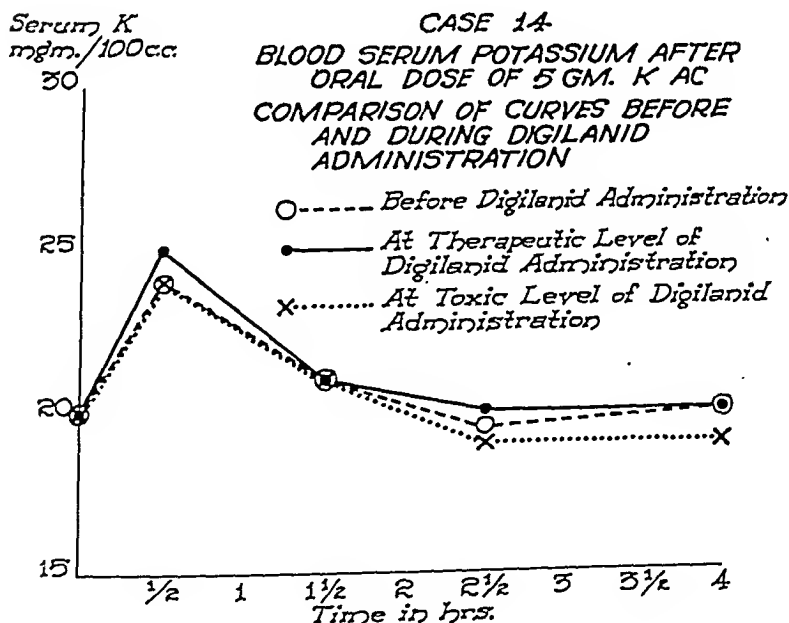


Fig. 3.

insulin. He associated their occurrence with a low potassium content of the blood serum. The fasting potassium content of the blood serum in our series varied from 16 to 20 mg. per cent, and there was apparently no correlation between this level and the presence or absence of ectopic beats.

There is a suggestion that the relative rise of the serum potassium from the fasting level to that which existed one-half hour later had more effect on the ectopic beats than the absolute potassium content (Cases 2, 3, 7, 13, and 16).

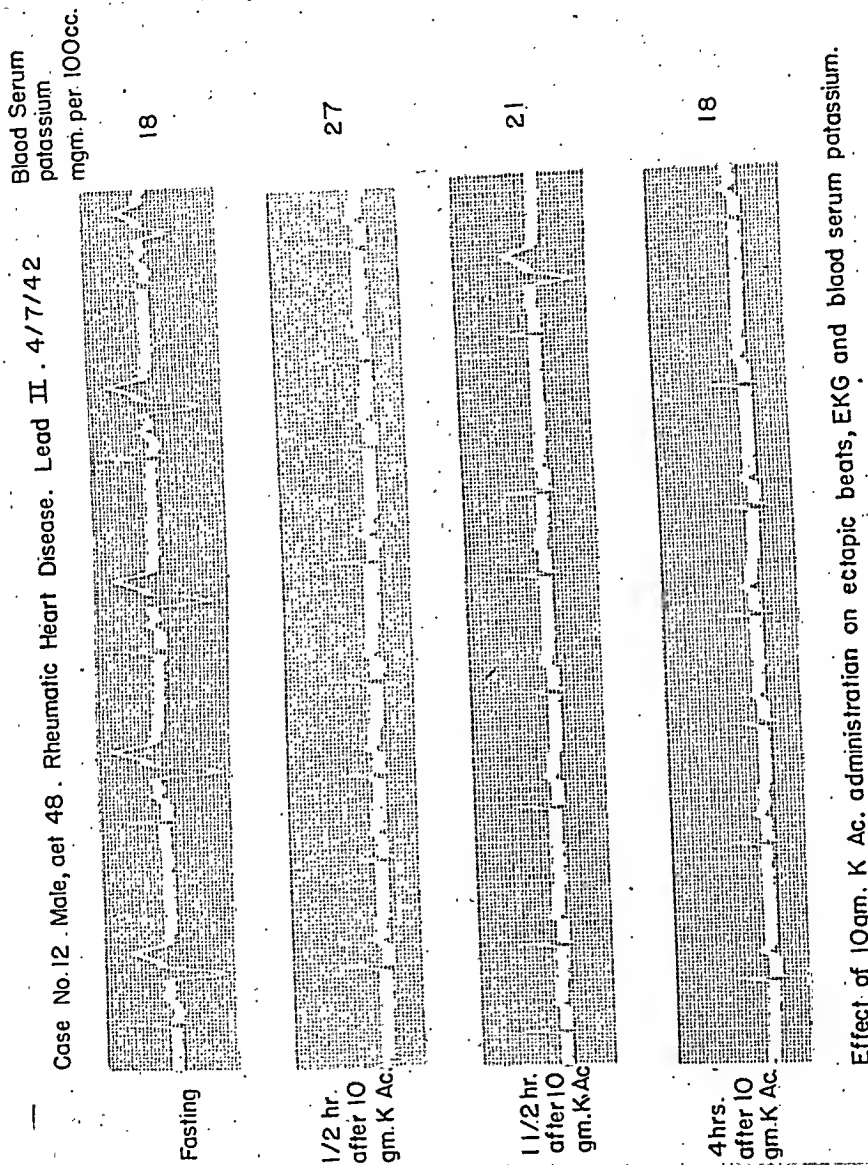


Fig. 4.

In Case 12 (Fig. 4), after 10 Gm. of potassium acetate had been given, the ectopic beats disappeared in one-half hour, at which time the serum potassium was at the unusually high level of 27 mg. per cent. When it fell, at the end of one and one-half hours, to a level of 21 mg. per cent, the ectopic beats reappeared, but disappeared again at the two and one-half hour and four hour periods, when the blood serum potassium content had resumed the fasting level. This was an instance

TABLE

A STUDY OF EIGHTEEN CASES ILLUSTRATING THE EFFECT OF POTASSIUM ON ECTOPIC BEATS

CASE	SEX	AGE	ETIOLOGY OF DISEASE	DATE	RHYTHM	DOSE OF DIGITALIS
1	L. C. Male	64	Coronary arteriosclerosis	8/5/41	Complete heart block (A-V)	Digld. 1 mg. daily x 12
2	J. L. Male	74	Coronary arteriosclerosis	8/15/41	Aur. fibrillation	Digld. 1 mg. daily 3+ weeks
3	M. G. Male	73	Coronary arteriosclerosis, hypertension	8/15/41	Sinus rhythm	Digld. 1 mg. daily 3+ weeks
4	T. L. Male	67	Coronary arteriosclerosis	8/6/41	Aur. fibrillation	Digld. 1 mg. daily x 10
5	J. O. Male	71	Coronary arteriosclerosis	8/29/41	Sinus rhythm	Digld. $\frac{1}{2}$ mg. daily 3+ weeks
6	W. L. Male	71	Coronary arteriosclerosis	8/29/41	Sinus rhythm	Digld. 1 mg. daily x 25
7	W. B. Male	80	Arteriosclerosis and coronary occlusion	9/9/41	Aur. fibrillation	Digld. 1 mg. daily x 37
8	C. S. Male	72	Coronary arteriosclerosis	9/9/41	Aur. fibrillation	Digld. 1 mg. daily 3+ weeks
9	C. S. Male	83	Coronary arteriosclerosis, angina pectoris	10/3/41	Sinus rhythm	None
10	J. G. Male	79	Coronary arteriosclerosis	12/27/41	Aur. fibrillation	None
11	H. B. Male	77	Coronary arteriosclerosis, hypertension	10/14/41 11/19/41 12/13/41	Aur. fibrillation Aur. fibrillation Aur. fibrillation	None Digld. $\frac{1}{2}$ mg. daily 3+ weeks Digld. 1 mg. daily x 24
12	F. S. Male	45	Rheumatic	11/10/41 1/13/42 4/5/42 4/7/42	Aur. fibrillation Aur. fibrillation with bigeminus Aur. fibrillation with bigeminus Aur. fibrillation with bigeminus	Dig. Fol. 0.3 for 3 days and then Dig. Fol. 0.1 Gm. daily x 30 Dig. Fol. 0.1 Gm. daily x 64 Digld. 2 mg. daily x 3 and then Digld. 1 mg. daily x 14 Digld. 1 mg. daily x 2
13	H. K. Male	76	Coronary arteriosclerosis ? rheumatic	10/14/41 11/19/41 12/24/41 4/6/42	Aur. fibrillation Aur. fibrillation Aur. fibrillation Aur. fibrillation	None Digld. $\frac{2}{3}$ mg. daily x 30 Digld. $\frac{1}{2}$ mg. daily x 14 Digld. $\frac{1}{2}$ mg. daily x 35 Digld. $\frac{1}{2}$ mg. daily x 60 Digld. 1 mg. daily x 43

BLOOD SERUM POTASSIUM IN MG. PER CENT IN RELATION TO TIME OF POTASSIUM DOSE					NO. OF VENTRICULAR ECTOPIC BEATS PER MINUTE IN RELATION TO TIME OF POTASSIUM DOSE					POTASSIUM ACETATE DOSAGE
FASTING	$\frac{1}{2}$ HR. AFTER	$1\frac{1}{2}$ HR. AFTER	$2\frac{1}{2}$ HR. AFTER	4 HR. AFTER	FASTING	$\frac{1}{2}$ HR. AFTER	$1\frac{1}{2}$ H.R. AFTER	$2\frac{1}{2}$ HR. AFTER	4 HR. AFTER	
19	16	24	21	—	15	2	0	0		5 Gm. orally
17	25	22	20	—	7	12	0	7		5 Gm. orally
17	27	23	—	—	10	0	0	0		5 Gm. orally
16	18	19	16	—	6	0	0	0		5 Gm. orally
17	—	22	18	—	35	3	0	4		5 Gm. orally
—	—	—	—	—	12	0	0	0		5 Gm. orally
16	30	19	17.5	17	25	0	0	0	0	5 Gm. orally
17	15	26	17.5	17	22	0	0	7	10	5 Gm. orally
20	—	—	—	22	1	0	0	0	0	5 Gm. orally
23	27	30	25	22	(Aur. ectopic beats only)					5 Gm. orally
20	22	25	—	19	0	0	0	0	0	5 Gm. orally
19	—	26	—	20	1	0	0	0	0	5 Gm. orally
21	—	30	—	—	0	0	0	0	0	5 Gm. orally
18	20	21	—	—	20	2	8	6	0	5 Gm. orally
18	20.5	18.5	—	—	40 Abolished for 6 minutes only after potassium injection.					1 Gm. intra-venously
18	20	20	—	18	Bigem. Bigem. Bigem. Bigem. Bigem.					5 Gm. orally
18	27	21	18	18	30	0	6	1	0	10 Gm. orally
17	26	25	19	18.5	3	1	3	2	0	5 Gm. orally
18	23	23	20	17	1	0	0	0	0	5 Gm. orally
17	23	19	18	17	0	0	0	0	0	5 Gm. orally
17	24	19	18	17	12	0	0	0	0	5 Gm. orally

TABLE I

CASE	SEX	AGE	ETIOLOGY OF DISEASE	DATE	RHYTHM	DOSE OF DIGITALIS
14	A. M. Male	78	Coronary arteriosclerosis	11/13/41	Sinus rhythm	Digld. $\frac{2}{3}$ mg. daily x 3
				2/5/42	Sinus rhythm	Digld. $\frac{2}{3}$ mg. daily x 84
				3/24/42	Sinus rhythm	Digld. $1\frac{1}{2}$ mg. daily x 10
15	J. B. Male	77	Hypertension	11/23/41	Sinus rhythm	Dig. Fol. 0.3 Gm. for 3 days Dig. Fol. 0.1 Gm. daily for 4+ weeks
16	A. A. Male	80	Coronary arteriosclerosis, hypertension	12/13/41	Nodal rhythm (A. V.)	None
17	J. R. Male	64	Coronary arteriosclerosis	4/23/42	Aur. fibrillation	Dig. Fol. 0.3 Gm. for 3 days
				4/25/42	Aur. fibrillation	Dig. Fol. 0.1 Gm. daily 3+ weeks
				5/10/42	Aur. fibrillation	No digitalis 15 days
18	J. B. Male	62	Coronary arteriosclerosis, rheumatic	5/16/42	Aur. flutter	8 c.c. Digld. C. intravenously
					Aur. fibrillation	4 doses of Digld. C.
					Aur. flutter	$\frac{1}{4}$ mg. each in 18 hours

of an apparent transient correlation of the blood serum potassium level with the loss of ectopic beats, but further confirmed the theory of later fixation of the potassium to the tissue. In all cases the ectopic beats had returned within sixteen hours. In one case (Case 12), giving 2 Gm. of potassium acetate in a 10 per cent solution intravenously caused the disappearance of ectopic beats for only six minutes, although the rise of potassium in the serum was not great.

Electrocardiograms were taken in most cases at approximately the same time as the blood specimens were obtained. In three instances studies were made before digitalis was administered, during the therapeutic period, and after the development of toxicity. In two other instances studies were made during the therapeutic period, either before or after the observations during a toxic phase. In Case 12 (Fig. 5), studies were made during repeated potassium administrations for forty-eight hours.

The electrocardiographic changes caused by the administration of potassium experimentally to cats (Chamberlain, et al.¹⁷), to dogs (Winkler, et al.¹⁶), to guinea pigs (Speelman¹⁸), and to man (Sampson and Anderson,^{1, 2} Stewart and Smith,²⁰ Thompson,^{14, 15} Castleden,¹⁰ and Keith, et al.,^{56, 57}) include elevation of the T waves, auriculoventricular block, intraventricular block, and various arrhythmias.

The changes observed in this series were relatively minor. Ten patients showed slight elevation of the T waves, five showed flattening and depression of S-T intervals, and five showed minor changes in the

—CONT'D

BLOOD SERUM POTASSIUM IN MG. PER CENT IN RELATION TO TIME OF POTASSIUM DOSE					NO. OF VENTRICULAR ECTOPIC BEATS PER MINUTE IN RELATION TO TIME OF POTASSIUM DOSE					POTASSIUM ACETATE DOSAGE
FASTING	½ HR. AFTER	1½ HR. AFTER	2½ HR. AFTER	4 HR. AFTER	FASTING	½ HR. AFTER	1½ H.R. AFTER	2½ HR. AFTER	4 HR. AFTER	
20	24	21	19.5	20	0	0	0	0	0	5 Gm. orally
20	25	21	20	20	0	0	0	0	0	5 Gm. orally
20	24	21	19	19	0	0	0	0	0	5 Gm. orally
19	24	20	19	19	0	0	0	0	0	5 Gm. orally
18	25	19	18	19	7	2.5	0	8	0	5 Gm. orally
					(Aur. ectopic beats only)					
17	19	20	18	18	—	—	—	—	—	5 Gm. orally
18	22	20	19	18	5	2.5	1	0	5	5 Gm. orally
27	25	—	—	—	5	0	0	—	—	10 Gm. orally
17	24	—	20	19	0	0	0	0	0	5 Gm. orally
18	26	24	23	19	8	0.5	6	2	0	10 Gm. orally

voltage or direction of the QRS complexes. These occurred with about equal frequency before and after digitalis administration, and with (Fig. 6, Case 13) and without ectopic beat formation (Fig. 7, Case 14).

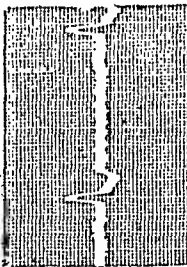
Another possible influence of potassium on the cardiac rhythm is illustrated by Case 18; the patient was a white man, aged 62 years, with rheumatic heart disease, who entered the hospital with auricular flutter. The flutter was supplanted by auricular fibrillation only after large doses of digilanid C intravenously and orally. Two and one-half hours after the administration of 5 Gm. of potassium acetate by mouth, the mechanism reverted to auricular flutter, with a variable degree (4:1 to 7:1) of auriculoventricular block. Not all of the ectopic beats had disappeared at this time. Four hours after the administration of potassium acetate, all of the ectopic beats had disappeared, and the flutter was regular, with 7:1 auriculoventricular block. Normal rhythm was later restored by giving 1 Gm. of quinine dihydrochloride intravenously.

Stewart and Smith²⁰ have recently reported certain toxic effects of the oral use of potassium chloride and potassium iodide in man which resemble those in dogs¹⁶ and cats.¹⁷ In some cases, doses of 2 to 8 Gm. per day produced auriculoventricular block, aberrant ventricular impulses, and auricular standstill.

Likewise, Arden⁵⁸ described paresthesias after 15 Gm. of potassium chloride or potassium carbonate had been given. This observation was confirmed by Keith, Osterberg, and Burchell,^{56, 57} who used oral doses

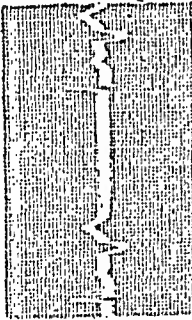
Case No. 12. Male, aet. 48. Rheumatic Heart Disease.

I

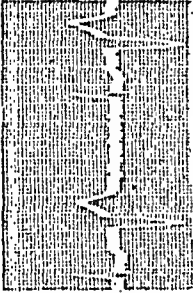


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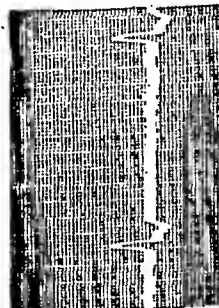
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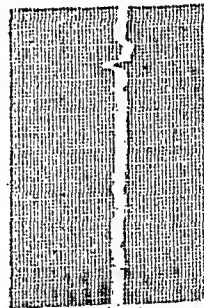
III



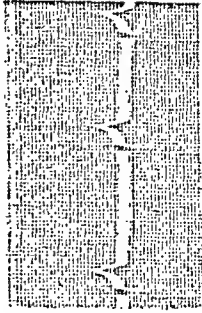
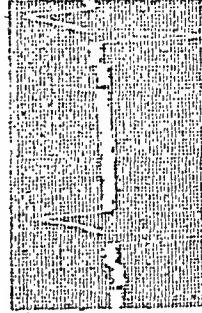
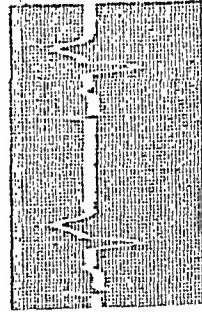
IV



6 hrs. after
last dose
5gm. K Ac
bid (15 gm.
total).
4/6/42



7 hrs. after
last dose
5gm. K Ac
bid (25gm
total).
4/7/42



Effect of repeated potassium administration on EKG in 48 hour period.

Fig. 5.

Digitalis Intoxication.

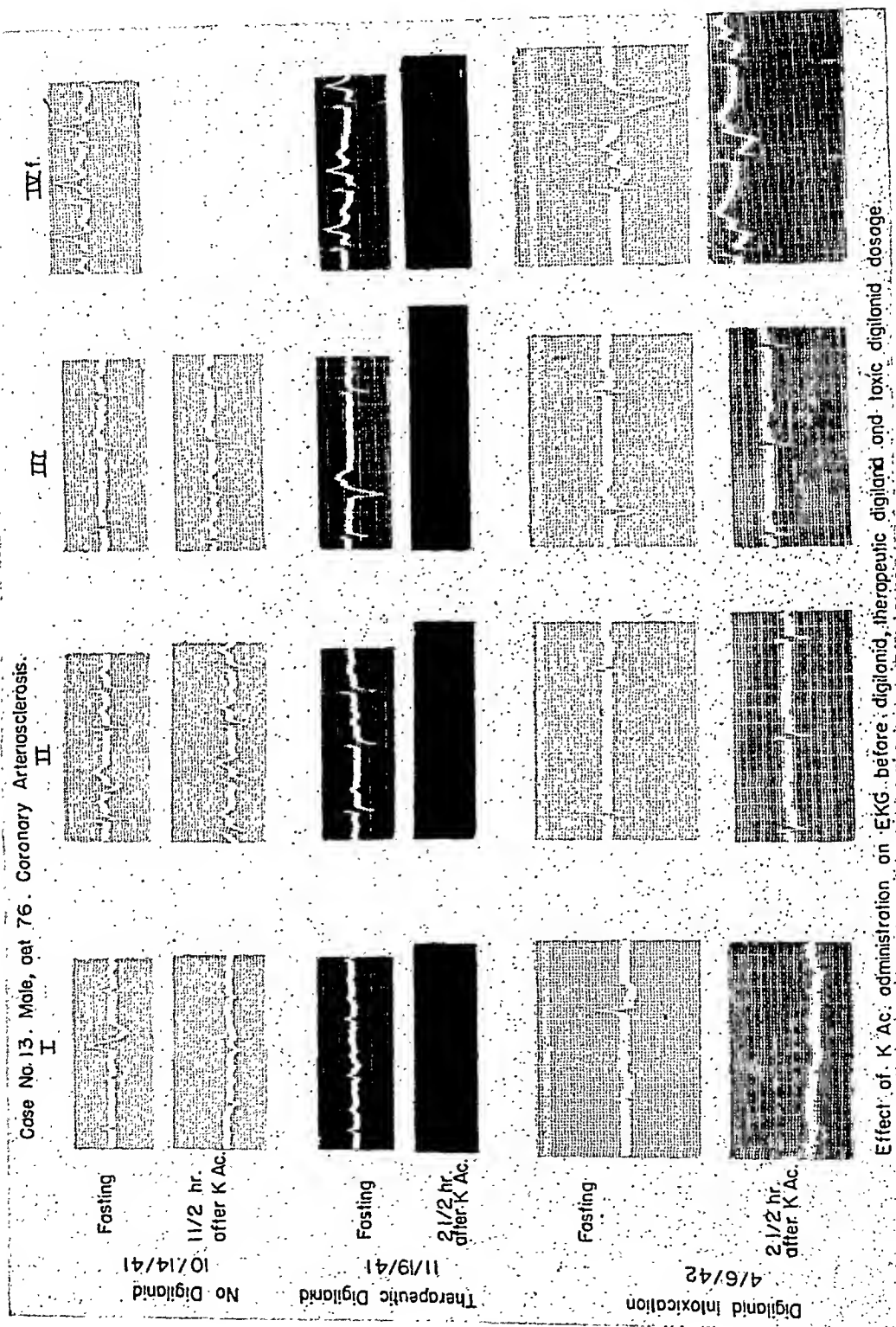


FIG. 6.

of 12.5 to 17.5 Gm. of potassium chloride, or potassium bicarbonate in an intravenous dose of 9.5 Gm. in a 1 per cent solution, administered over ninety minutes. They considered 30 mg. per cent of blood serum potassium as the level at which certain paresthesias appear. In one case, not included in our series because of lack of potassium studies, paresthesias preceded severe shock-like symptoms after a 5 Gm. dose of potassium acetate had been given intravenously. There have been previous reports of serious shock-like symptoms after the oral administration of potassium salts to patients with kidney disease (Smillie,⁵⁹ Wilkins and Kramer,⁵⁴ Blum,⁶⁰ Magnus-Levy,⁶¹ and others). The absence of nitrogen retention and clinical manifestations indicated that none of our patients had severe kidney disease.

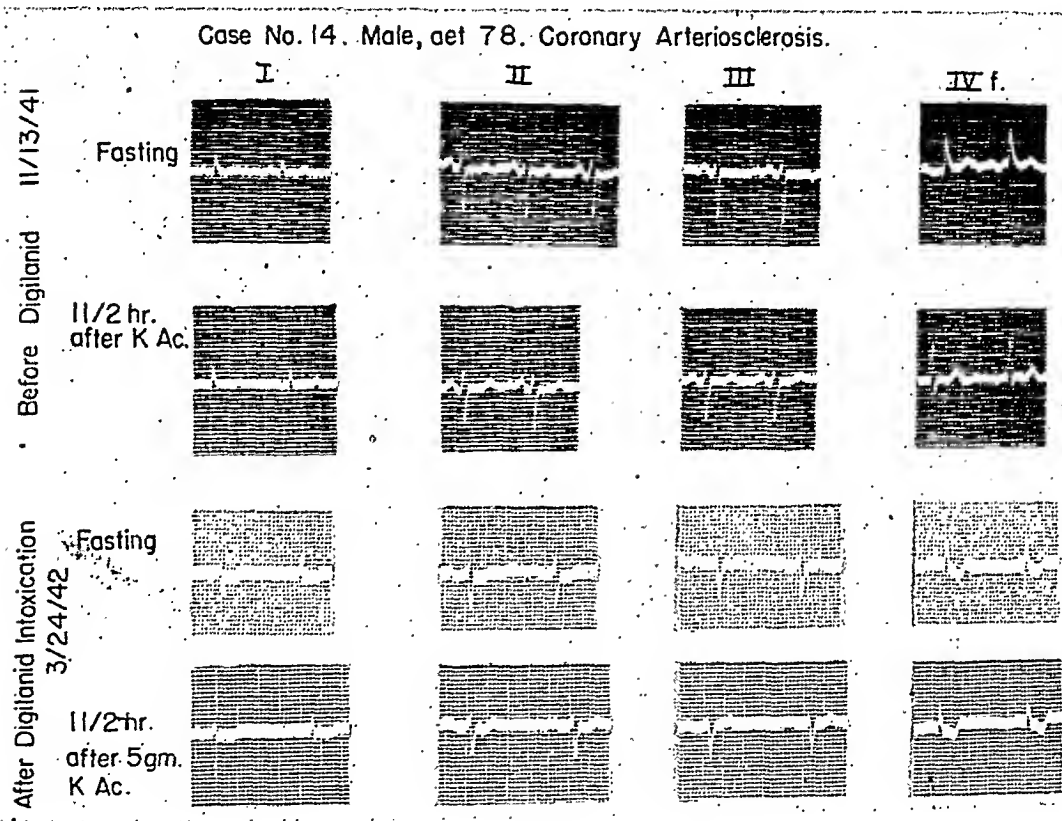


Fig. 7.

In the report of Sampson and Anderson^{1, 2} there were three instances of a paradoxical action of potassium which increased the number of extrasystoles; this may be interpreted as a toxic phenomenon. These patients did not have digitalis intoxication.

In the present series of cases no signs of serious intoxication or paradoxical action occurred with the oral administration of 5 to 10 Gm. of potassium acetate, or in one instance after the intravenous injection of 1 Gm. of potassium acetate in a 10 per cent solution at a rate of 1 c.c. per minute. In one other instance, as previously mentioned, severe shock-like symptoms occurred after the injection of 10 c.c. of a 50 per cent potassium acetate solution at a rate of 1 c.c. per minute.

Although the purpose of this work was not to investigate the therapy of digitalis intoxication, it may be assumed that the oral administration of potassium salts will abolish ectopic beats, and probably paroxysmal ventricular tachycardia. Sampson and Anderson^{1, 2} reported the cessation of paroxysmal ventricular tachycardia after potassium therapy in a patient with coronary arteriosclerosis who had not received digitalis, which suggests that potassium might be efficacious in the treatment of ventricular tachycardia caused by digitalis intoxication.

Although no amelioration of other toxic symptoms, e.g., nausea, was brought about by the use of potassium in this series of cases, the salts were administered for too short a time to draw any definite conclusion on this point.*

CONCLUSION

We have shown that the ectopic beats caused by digitalis can be abolished in every instance by the oral administration of potassium salts in doses of 5 to 10 Gm.; this is in contrast to the observation of Sampson and Anderson that only 50 per cent of ectopic beats from other causes were affected by potassium salts. We thus present positive evidence that the disturbance of potassium balance in the heart muscle is related to digitalis administration—at least in toxic doses.

There was no correlation between the presence or absence of ectopic beats and the fasting blood serum potassium level. No significant differences occurred in the curves of the potassium rise and fall in the blood serum in relation to oral potassium acetate doses at any stage before or during digitalis administration—even with toxic doses.

When ectopic beats were abolished by the administration of potassium, they failed to return in many instances until long after the blood serum potassium content had fallen to fasting levels. This suggests that potassium had become fixed to, or had altered the state of, the cardiac muscle, for the presence of ectopic beats, temporarily at least, was not influenced by the potassium content of the blood serum.

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EMBOLISM AND SECONDARY THROMBOSIS OF THE BIFURCATION OF THE AORTA

- A. CORONARY OCCLUSION WITH ENDOMYOCARDIAL INFARCTION
- B. MITRAL STENOSIS WITH ATRIAL FIBRILLATION

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THE recognition of potential causes, precipitating factors, and especially of the secondary complications of progressive thrombotic processes, as well as the prompt diagnosis and localization of acute arterial obstruction, has come to a position of considerable importance now that prevention and treatment of the condition are much more promising. Cases of saddle embolus at the bifurcation of the aorta and embolism of the common iliaes and femoral arteries should be reported in detail, so that the etiologic factors and the clinical and the pathologic manifestations may be established clearly. Attention should be focused on the possible seriously complicating secondary thrombotic processes.

Secondary thrombosis is an essential consideration, whether conservative management or embolectomy be undertaken. The prompt use of antispasmodics (papaverine) intravenously, alone or with an anticoagulant (heparin), followed by passive vascular exercises (pavaex), may be immediately effective, and opening up of the major arterial pathways may be the result—a most spectacular therapeutic triumph. At least, the serious complications can often, in a large measure, be prevented.

Heparinization, to be effective, must be instituted before the secondary thrombosis takes place, and, certainly, as soon as possible after an embolus has lodged, in order to prevent the local development of thrombosis. This is particularly so in patients who are likely to have atheromatosis of the aorta. Immediate diagnosis is, therefore, of considerable importance. The prognosis is worse in cases of coronary thrombosis and hypertension than in patients with mitral stenosis.

The larger the embolus, the higher up in the vascular tree it lodges, and, the more completely it fills the lumen, the greater are the dangers of complications. In the presence of an effective heparin, liquaemin, or dicumarol action, conservative methods, such as the intravenous injection of papavarine ($\frac{1}{2}$ to 1 grain), as suggested by Denk, and passive vascular exercise, as employed by L. G. Herrmann, may be hopefully undertaken. This should yield results during the first six hours after the occurrence of embolism. Medical treatment should probably be instituted first in every case.

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Early diagnosis and localization are as important in successful surgical treatment as they are in conservative management. Embolectomy is most successful only within the first six hours, and, at the latest, twenty-four hours after the accident.

SUMMARY OF REPORTED RESULTS OF TREATMENT

Medical treatment, conservative and expectant, with morphine, whiskey, and pavaex therapy has been reported as successful. L. G. Herrmann¹ has had three successes with conservative management among several unpublished cases of saddle embolism. Morris² also reported success in a case of embolism of the bifurcation of the aorta in which pavaex therapy was started forty-eight hours after the onset. This may have been a spontaneous recovery.

Fry³ reviewed 135 reported cases of embolism of the bifurcation of the aorta. In this series there were twenty survivals, of which ten were attributed to the development of collateral circulation. Nine recoveries were believed to have been the direct result of embolectomy, and one was attributed to the passage peripherally of the embolus.

Surgical removal of an embolus and subsequent complete restoration of the circulation has been successfully accomplished. In Sweden, up to 1936, 382 embolectomies had been performed, with 86 (22.5 per cent) recoveries; 69 patients (18.1 per cent) required subsequent amputation, and 227 (59.4 per cent) died in the hospital. Of the 17 patients with aortic embolism, 3 (17.7 per cent) were resected, and of 66 with iliac embolism, 10 (15.1 per cent) were saved by operation. In England, up to 1937, there had been only 20 embolectomies, with only 11 (55 per cent) recoveries. These series were done before any anticoagulant was generally available. Since the introduction of heparin for clinical use, slightly over half of the first 100 patients operated upon have recovered.

Although the bifurcation of the aorta is less accessible than large peripheral arteries, it has been completely cleared of clots from below. In a young patient with mitral stenosis, McMaster⁴ succeeded in removing emboli from both iliac bifurcations and re-establishing the circulation without the use of anticoagulants. McFarland⁵ has successfully removed saddle emboli directly, and Ravdin and Wood⁶ cleared the bifurcation of the aorta of clots indirectly, through the femorals, with the help of heparin.

Murray⁷ reported sixteen surgical successes, with nine complete successes, in a series of seventeen embolisms in accessible major arteries. In Murray's series of thirty-seven cases of embolism, more than half of the emboli were lodged in the common femorals, and four were arrested at the bifurcation of the aorta.

PREDISPOSING FACTORS AND COMMON SOURCES OF LARGE PERIPHERAL ARTERIAL EMBOLI

Arterial embolism is a possible complication in any case of organic disease of the heart or aorta. It has long been recognized that especially

patients with the atrial stasis of mitral stenosis and atrial fibrillation, and those with verrucose valvulitis, are candidates for embolism. Mural thrombi that developed in the greatly dilated left auricle and ventricle during chronic failure are occasionally loosened and carried into the aorta as emboli. Mural thrombi that accumulate on the endocardium beneath recent myocardial infarcts are more common sources of emboli. The statistics of the incidence of arterial embolism from these various sources are as yet incomplete. All cases should be reported in order to accumulate data on the frequency of the condition.

Garvin⁸ found mural thrombi in the heart in one-third of all cases in which death was caused by congestive heart failure, and in two-thirds of the hearts with myocardial infarction, in a study of 771 consecutive autopsies on patients who died of heart disease.

Solandt, Massil, and Best,⁹ on the premise that 10 per cent of the deaths of patients with coronary thrombosis were caused by embolism as a result of mural thrombus formation, undertook experiments on dogs. They studied mural thrombus formation that resulted from ligation of the anterior descending branch of the left coronary artery and subsequent injection of sodium ricinoleate into the left ventricular cavity. They found that in such experiments mural thrombus formation could be regularly prevented entirely by the use of heparin.

Embolism from the left side of the heart to the aortic bifurcation, along with secondary local thrombosis, was recognized by Allibert, in 1828, and by Alexander, in 1905, and elaborated upon by Welch, in 1909. Welch's¹⁰ series consisted of 59 cases; in 35, the heart was the source, and, in 20 of these, rheumatic mitral stenosis was present; whereas, in 3, acute mitral endocarditis was the primary etiologic factor. Hesse,¹¹ in a review of the literature on 72 cases up to 1921, considered embolism and thrombosis of the bifurcation of the aorta together. Rothstein,¹² in 1935, reviewed the literature on 125 cases of saddle embolism of the aorta. He added 5 cases of his own in children following acute infections, one from iodoform poisoning, and one from tumor pressure.

Mural thrombi of the aorta have been considered generally as rare sources of embolism at the aortic bifurcation, but in several of Welch's,¹⁰ Hesse's¹¹ and Rothstein's¹² cases the emboli came from the aorta or an aneurysm, or were caused by a mycotic aneurysm, tumor pressure, or atheromatosis. Thrombi in the thoracic aorta are more common sources of embolism of the superior mesenteric or the renal arteries, as well as of the arteries of the lower extremities. Thrombi on the endocardium of the right ventricle, as well as from the great veins, may give rise to embolism of the pulmonary arteries, and cause acute cor pulmonale.

THE CLINICAL PICTURE

Premonitory symptoms may occur as a large embolus migrates down the aorta, and may well be watched for in patients who are predisposed to such complications. *Abdominal cramps* at higher, then lower,

levels, with nausea, vomiting, meteorism, and constipation, may indicate temporary closure of the mesenteric and renal orifices. After localization, the clinical picture is quite characteristic, especially if there is sudden and complete occlusion in a major arterial pathway. The sudden onset of *pain*, localized to the region of the obstruction, is the first symptom. The pain is not always excruciating, but is frequently severe, and produces what seems to be temporary paraplegia; occasionally it is moderate in character. In cases of only partial obstruction of large vessels, such as the iliacs or the aorta at the bifurcation, the immediate local pain may be mild, and, in stolid persons, may go unrecognized. It is practically impossible to differentiate between embolism and thrombosis at the aortic bifurcation. If the obstruction is fairly complete, paresthesias, tingling, formication, *numbness*, and *coldness* are usually felt in the extremities, beginning at the distal ends and migrating upward as far as the level of the iliac crests. Later on, with the numbness and coldness, there is pain. Contraction of the leg muscles is often accompanied by pain which is relieved by rest, as in intermittent claudication.

The *color changes* occur promptly below the site of the embolus. Striking pallor appears immediately in the distal parts. There is cadaveric whiteness, and the skin takes on a somewhat waxy appearance. As one proceeds up the extremity from the tips of the digits, a zone of dark cyanosis is noted on the pallid background. Above this there is a zone of mottled skin, with patchy, pallid, and purplish areas which extend to the level of the embolus.

When the embolus is lodged at the bifurcation of the aorta, color changes are present as high as the lower quadrants of the abdomen. If the embolus is at the common iliac bifurcation, color changes extend into the upper third of the thigh; if in the common femoral bifurcation, color changes reach the lower two-thirds of the thigh; if in the popliteal bifurcation, the color changes appear between the ankle and the knee; if in the posterior tibial artery, color changes are limited to the heel and the plantar surface of the foot below the instep.

A *lowered skin temperature* is noted on palpation. Usually the skin is stone-cold to the touch. Variations of coolness are observed up to the level of the occlusion. Absence of pulsation in the dorsalis pedis, posterior tibial, popliteal, and femoral arteries of both legs and a zero *oscillometric index* in both legs and thighs result from saddle embolism or thrombosis of the bifurcation of the aorta or both common iliaes.

The *skin sensitivity* is reduced. The reflexes are decreased or absent, and voluntary control of the movements of the toes is lost. A saddle embolus may produce complete obliteration on one side and only partial obstruction of the other iliac. A murmur may be heard over a partially obstructed artery. Small fragments may break off of the main embolus and lodge at a bifurcation further distally, especially when the main artery is only partially obstructed.

When occlusion of an artery by an embolus is incomplete, the diagnosis may be most difficult, as one might expect. In such cases the disease frequently goes unrecognized clinically unless particularly looked for. In two of Fry's³ cases the diagnosis was not made until months after the onset. In a third case it was found unexpectedly at autopsy.

OUR CLINICAL MATERIAL

Data on five cases of saddle embolus at the bifurcation of the aorta, with one recovery, and complete autopsy studies in three cases are herewith presented. The first two cases were in elderly males with hypertensive arteriolar disease, atheromatosis, coronary thrombosis, endomyocardial infarction, and mural thrombi. These gave rise to emboli which lodged at the bifurcation of the atheromatous aortas, followed by secondary thrombosis. The intra-aortic thrombosis extended backward practically to the levels of the renal arteries, and distally into the iliaes.

The third case was that of an elderly woman with rheumatic mitral stenosis and insufficiency, atrial fibrillation, vegetative endocarditis, hypertensive arteriolar disease, and mural thrombi in all of the heart chambers. An embolus, probably originally from the left atrium, saddled the bifurcation of her aorta. Marked arteriosclerosis of the aorta near the bifurcation apparently was responsible for prompt, massive, secondary thrombosis.

The last two cases were in younger persons with rheumatic mitral stenosis and insufficiency and atrial fibrillation. They apparently had less aortic disease and apparently survived longer after the emboli lodged at the aortic bifurcation. Both subsequently had cerebral embolism; one died and one survived. Conservative medical treatment was used in all instances. Heparinization and surgical intervention would probably have been successful in some of the cases.

CASE REPORTS

CASE 1. *Coronary Occlusion, Transient Atrial Fibrillation, Endomyocardial Infarction, Mural Thrombosis, Saddle Embolism of the Bifurcation of the Aorta, With Secondary Thrombosis and Gangrene of the Right Foot, Encephalomalacia.*—J. B., No. 36370, a 36-year-old Negro, was admitted to the John Sealy Hospital March 31, 1941, complaining of severe substernal pain radiating down the left arm; the pain had lasted for two hours. The patient was in shock, and was sweating, prostrated, cold, and clammy; his blood pressure was 90/50. His heart was apparently not enlarged. The heart sounds were distant. The abdomen was negative. The liver was not enlarged or tender. There was no edema.

The electrocardiogram confirmed the clinical diagnosis of coronary thrombosis, with posterior myocardial infarction. The cardiac mechanism, which was normal on first examination, changed within half an hour after admission to atrial fibrillation, with many ventricular ectopic beats. Within three hours after quinidine therapy was begun (total dose, $13\frac{1}{2}$ grains), regular sinus rhythm was re-established. The evidences of shock decreased. The blood pressure rose to 110/90; pure oxygen had been given through an aviator's mask during this time.

Small doses of morphine were required occasionally during the first three days for relief of chest pain. For several days after admission there was some difficulty with gaseous abdominal distention. No signs of congestive heart failure developed at this time, and the first two weeks of his course were fairly uneventful.

On the morning of April 16, he began complaining of pain of rather sudden onset in the abdomen and right flank, and of numbness of the toes, and coldness of the feet. Examination showed marked abdominal distention; there was definite tenderness in the costovertebral angle. Coolness of the skin of the lower extremities, especially below the knees, was conspicuous. No pulse could be felt in either femoral artery. The sense of touch, pain, temperature, and position was not impaired, and there was no paralysis. The diagnosis was left ventricular mural thrombosis, from which an embolus arose and lodged at the bifurcation of the aorta.

On April 18, oseillometric studies showed no pulsation in either thigh or leg. There had been increasing pain in the thighs and the coldness below the knees became more pronounced. Paravertebral sympathetic block was not effective in relieving pain or in restoring warmth to the leg. By the next day the pain had become relatively slight, but numbness of the toes and marked coldness of the legs below the knees persisted. The body temperature increased from normal to as high as 102° F. on April 18.

During the next four weeks the patient's course was rather uneventful. There was minimal pain in the legs, with no ulceration or gangrene. However, he continued to have a low-grade fever, reaching 101° F., rectally, daily for a week; thereafter his temperature rose only slightly above 100°. Secondary thrombosis at the bifurcation of the aorta was suspected, but there was no clinical proof of extension of the process.

On May 19, postural exercises were instituted. On May 25, he developed a temperature of 103°; on May 26, his oral temperature reached 105°, and there was marked swelling of the right leg. On May 27, he suddenly complained for the first time of marked dyspnea, and died within a few minutes.

Summary of Pathologic Charges (Autopsy No. 5424).—The right leg was swollen and dark purple in color, and the epidermis lay loosely on the underlying tissue. Rigor mortis, which was present elsewhere, was absent from this leg. There was slight clubbing of the finger tips. The left pleural cavity was obliterated by fibrous adhesions; the right pleural cavity contained only a few fibrous adhesions. The pericardial sac contained 50 c.c. of clear yellow fluid.

The heart weighed 370 grams. The myocardium was flabby (Fig. 1). On cut section the posterior wall and apex of the left ventricle presented a mottled appearance, with areas which were yellow, dark red, and gray. Attached to the left ventricular endocardium over these infarcted areas there was a large, friable, red and gray thrombus. The coronary ostia were patent, but greatly narrowed by atherosclerotic and syphilitic changes. The interventricular branch of the left coronary artery was occluded by a large, firm, gray thrombus, located 1 cm. from the ostium. The circumflex branch was narrow, but patent; its intima bore a few atheromatous plaques. The right coronary artery contained a linear, firm, adherent, yellowish-gray thrombus. The thrombus did not occlude the lumen, but it extended into, and occluded, the interventricular branch of the artery.

The arch of the aorta presented longitudinal wrinkling and scattered stellate scars on the intimal surface, i.e., advanced syphilitic changes. There was moderate atherosclerosis which was most pronounced in the lower portion of the aorta. The lumen of the last 10 cm. of the abdominal aorta was occupied by a dark, red and gray, friable thrombus which was attached to the intima. This was more extensive as traced downwards, and completely occluded the aorta only at the bifurcation. The thrombus extended into both common iliac arteries, and from these into both internal and external iliac arteries. Separate from this thrombus there was a ring-

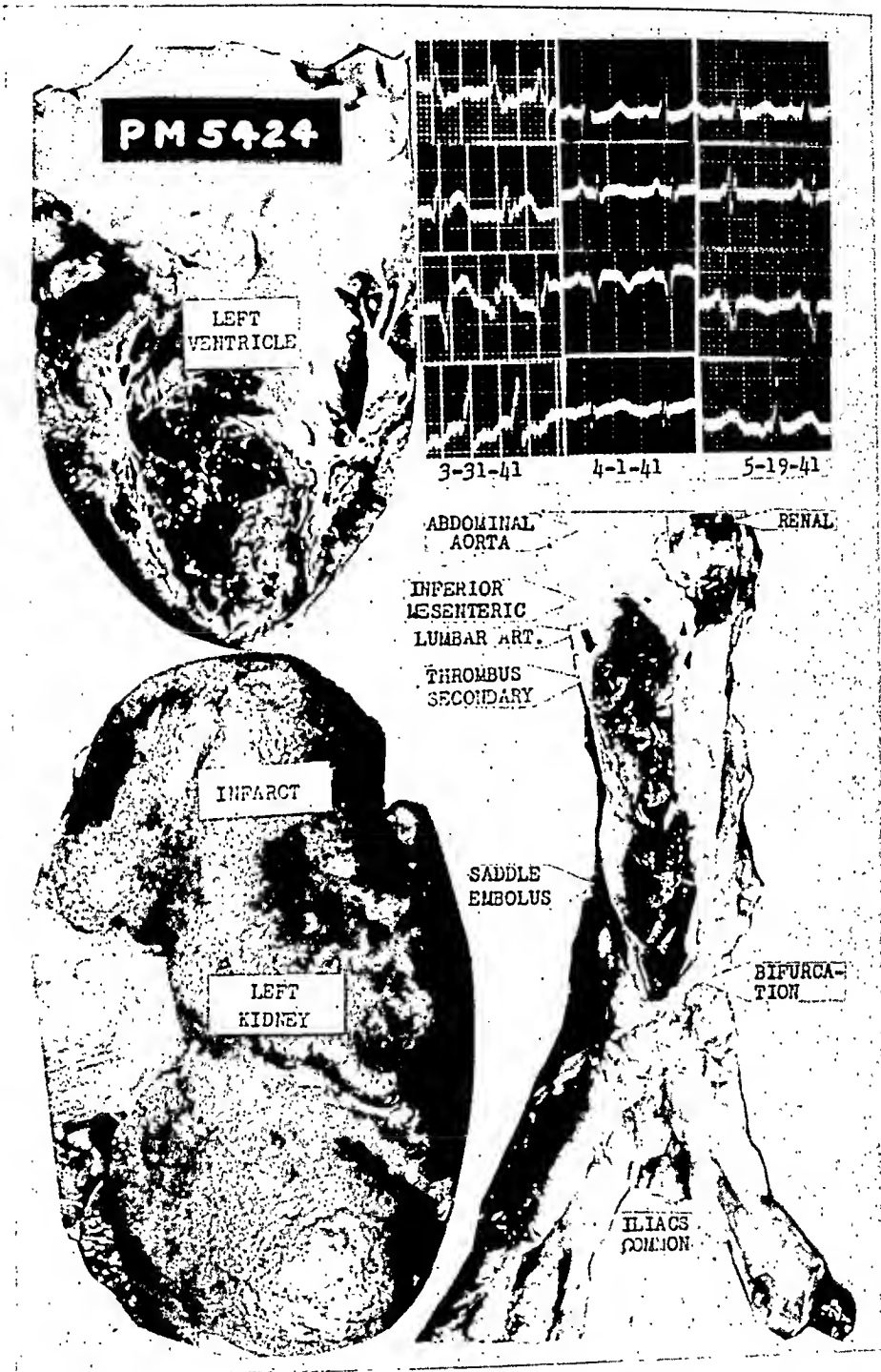


Fig. 1.—Case 1. J. B., J. S. Hospital, No. 36370; Post Mortem, No. 5424.
 Right upper: Electrocardiograms from above downward (Leads I, II, III, and IV F): March 31, 1941, showing atrial fibrillation and evidences of acute posterior myocardial infarction; April 1, 1941, normal sinus mechanism after 20 grains of quinidine sulfate, elevated S-T₁ and S-T₂ with negative T₂ and T₃; May 19, 1941, persistence of some residua of the posterior myocardial infarction.

Left upper: Aorta and left ventricle opened up to show the mural thrombus and the thinned myocardium.

Left lower: The infarcted left kidney.

Right lower: The aorta with the thrombus extending from 10 cm. above the bifurcation into both common iliacs.

shaped thrombus attached to the intima of the aorta around the origin of the left renal artery. The right common iliac vein also contained a thrombus. The splenic artery contained a thrombus near its origin, but was not completely occluded; the spleen did not show evidence of infarction. Microscopic sections of the aorta showed fragmentation of the elastic tissue of the media, vascularization of the media, and perivascular round cell infiltration of the adventitia, all of which are characteristic of advanced syphilitic aortitis. Sections of the iliac vessels showed that the thrombi were undergoing beginning organization; there was an acute inflammatory reaction about the vessels.

The right lung weighed 600 grams; the left, 580 grams. Both were markedly edematous and showed gross and microscopic evidence of chronic passive congestion. No emboli were demonstrable in the pulmonary arteries. The liver weighed 1,580 grams and showed marked chronic passive congestion. The right kidney weighed 210 grams, the left, 200 grams. Both kidneys appeared to be congested. Their cortical surfaces were roughened by many depressed scars, the largest of which measured 2 cm. in diameter. On cut section, the areas corresponding to the scars showed yellowish mottling. The corticomedullary line was indistinct. Microscopic section revealed old and recent areas of infarction. In the noninfarcted areas there was advanced arterial and arteriolar nephrosclerosis. The sclerosis of the arteries and arterioles was very pronounced.

The brain weighed 1,350 grams. The frontal poles appeared atrophic. The basal vessels were sclerotic. On section, both lateral ventricles were slightly dilated. In the right hemisphere, extending from the middle portion of the temporal lobe toward the occipital pole, there was a large area of old softening which involved the hippocampal, lingual, and lateral occipital gyri. The left hemisphere also showed a softened area; it was less extensive than that on the right, and involved, mainly, the lateral surface of the occipital lobe. On microscopic examination both softened areas showed organization and extensive scavenger cell formation. No emboli were demonstrable in the cerebral arteries.

CASE 2. Coronary Occlusion, Endomyocardial Infarction, Mural Thrombosis, Saddle Embolism of the Bifurcation of the Aorta, With Secondary Thrombosis, Gangrene of the Right Foot, Massive Infarction of the Kidneys, Uremia.—R. F., No. 72578, a 47-year-old white man, an oil field worker, was admitted to the John Sealy Hospital, Sept. 8, 1941. He had considered himself in good health until July 13, 1941. At that time he developed severe precordial pain radiating to his left arm. The pain lasted about one day, and required several hypodermic injections of morphine for relief. This treatment was carried out in a hospital in his home town. One week after the onset of the cardiac pain, he developed a cough and high fever, and was thought to have pneumonia. There was no hemoptysis. Two weeks after the onset of his pain he developed coldness and pain in his left leg. This was followed within a day by similar pain and coldness in his right leg. He was told that his symptoms were due to "milk leg." However, there was never any considerable swelling of either leg at any time. Coldness and slight pain persisted in both legs intermittently thereafter. The symptoms would become quite mild and tolerable as long as the patient remained in bed, but any attempts to get up caused an increase in pain.

Two weeks before his attack of cardiac pain, and about three weeks after the onset of the pain in his legs, there was a marked increase in the pain in his left foot; this subsided somewhat six weeks after the onset of the trouble, one week before admission. Pain, coldness, and blueness became severe in his right leg. The symptoms in his right foot continued, and, twenty-four hours before admission, it was noted that his whole right foot was stony cold and of a deep purple color. Large doses of morphine had been required in the twenty-four hours before admission to control the pain.

After the second day of his illness the patient had no further chest pain. There was no dyspnea at any time, or any history of congestive failure or angina pectoris previous to July 13. There was no family history of cardiovascular disease. No past history suggestive of peripheral vascular disease was elicited.

Physical examination on admission showed a slightly obese, lethargic (morphine), mildly disoriented, acutely ill, middle-aged white man with a temperature of 100° F., pulse rate of 90, respiration rate of 22, and blood pressure of 158/96. Examination of the head and neck was negative. The fundi were negative. The neck veins were not distended. The heart showed no appreciable enlargement to percussion. The tones were of good quality. No murmurs were heard. There was no gallop rhythm. The pulse was regular. Examination of the lungs was negative. Abdominal palpation was likewise negative. The liver was not palpable.

The extremities showed much evidence of disease. The right foot was slightly swollen. A fairly sharp line of demarcation was present between the blue and white skin just above the ankle. Sensitivity to touch and pain was present down to, but not including, the tips of the toes. The left foot was warm; it was somewhat paler than normal, although there was some faint pinkness of the skin. On first examination, no pulse could be felt in the dorsalis pedis, posterior tibial, or femoral arteries. Very careful palpation showed what was thought to be a faint femoral pulse bilaterally. The oscillometric indices were very low in the thighs and absent in either calf.

The electrocardiograms were of the Q_2 , T_2 , Q_3 , T_3 type, indicating residua of posterior myocardial infarction. On admission, there was only slight albuminuria. The erythrocyte count was 4,820,000, the leucocyte count, 9,450, and the hemoglobin, 76 per cent. The differential leucocyte count was normal. The Wassermann reaction and Eagle flocculation tests were negative. The blood urea nitrogen was 18 mg. per cent.

The patient was treated by paravertebral injection of the lumbar sympathetics. Ten c.c. of a 1 per cent novocain solution were injected into the second, third, and fourth lumbar spaces on the right. There was possibly very slight relief of pain after the injection. Pavaex therapy was used for twelve to fifteen hours a day on the right leg.

After several days it became quite obvious that attempts to save the right foot were futile, and amputation was done in the midthigh region. On Sept. 19, it was noticed that there were a large, bluish-red discoloration and considerable tenderness of the skin over the right buttock and sacrum. This lesion finally broke down and became a large decubitus ulcer.

The amputation stump healed satisfactorily without infection. There was some coldness of the left foot postoperatively, but this disappeared when the patient's state of shock was overcome. Throughout his hospital stay he ran a low-grade fever, with some increase from the time his decubitus infection started until a drainage of the ulcer was established. He experienced no recurrence of the pain in his chest. There was no evidence of congestive failure at any time during his hospital stay.

On Oct. 2, 1941, two weeks after operation, he rather suddenly developed a cramping abdominal pain, associated with nausea and vomiting. The symptoms at the time were considered to be suggestive of mesenteric embolism. There was, however, no diarrhea or melena, and migration of a large saddle embolus in the lower aorta was suspected. The abdominal pain subsided promptly after the administration of 1 grain of codeine and 10 grains of aspirin. On Oct. 6 the patient developed rather marked pain in his back, first in the left lumbar region, and later bilaterally. Then he suddenly became uremic, and the blood urea nitrogen rose to 150 mg. and the nonprotein nitrogen to 200 mg. per cent. On Oct. 17, the patient passed approximately 500 c.c. of highly colored, cloudy urine which

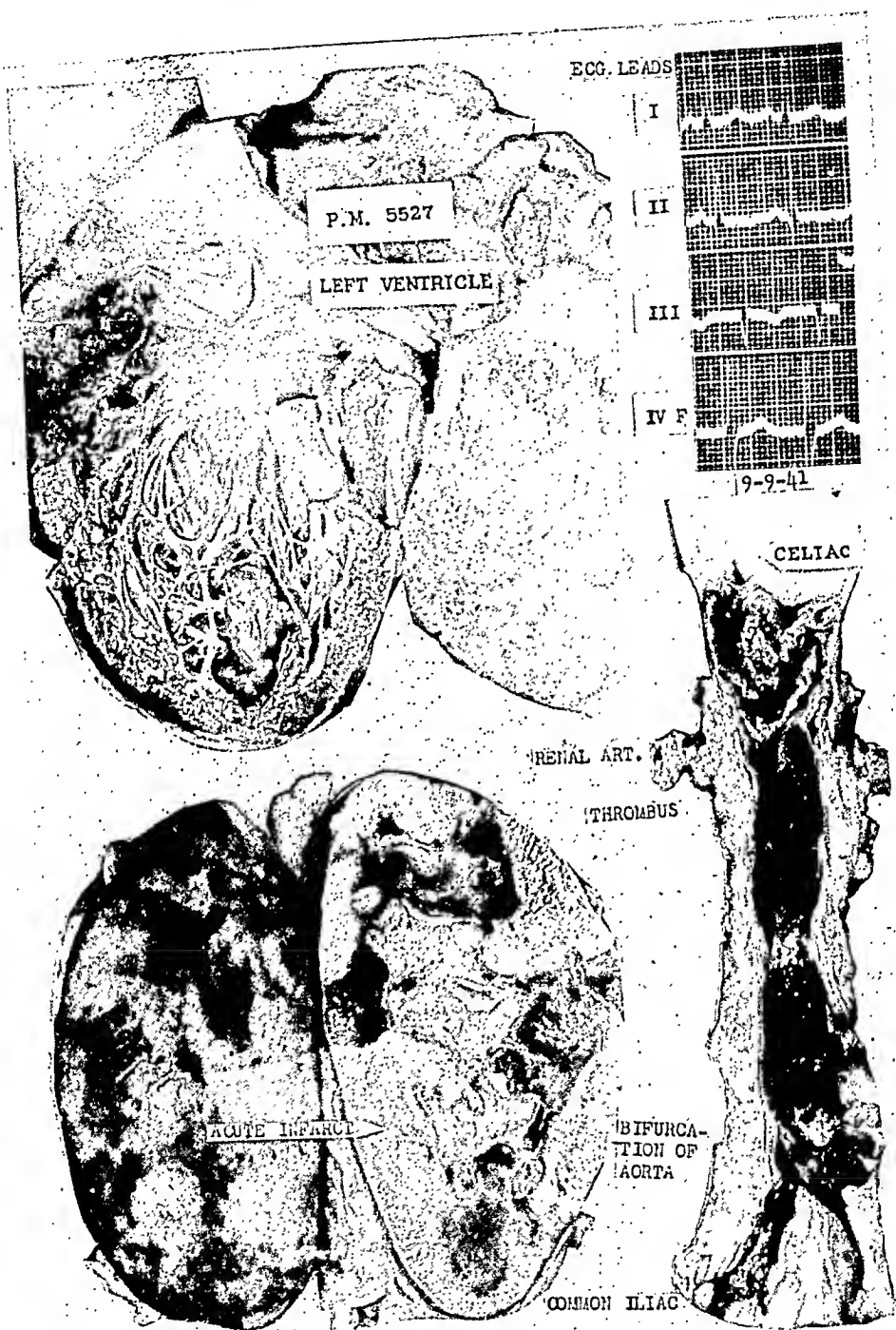


Fig. 2.—Case 2. R. F., J. S. Hospital, No. 72578; Post Mortem, No. 5527.
 Right upper: Electrocardiogram showing residua of posterior myocardial infarction; Q₂ and Q₃ and slightly negative T₂ and sharply negative T₂.
 Left upper: Aorta and left ventricle opened to show the mural thrombus and thinning of the muscle wall.
 Left lower: The massively infarcted right kidney.
 Right lower: The aorta containing the thrombus, extending from the celiac artery level into the common iliacs, especially on the right.

contained much albumin. This was virtually all the urine passed from Oct. 6 until his death, in uremia, without convulsions, on Oct. 20.

Summary of Pathologic Changes (Autopsy No. 5527).—The right leg had been amputated. There was sloughing over the right buttock and sacral region, with slight pitting edema of the left leg. The pleural cavities contained numerous thin fibrous adhesions which were easily broken down. The pericardial sac contained 300 c.c. of clear straw-colored fluid. The pericardial surfaces were covered with a thin layer of partially organized plastic exudate. The peritoneal cavity contained 1,400 c.c. of clear straw-colored fluid. There was generalized arteriosclerosis.

The heart weighed 440 grams (Fig. 2). All of the chambers contained mural thrombi. The thrombi in the ventricles were firmly attached to the endocardium at the site of a healing infarct involving the apices of both ventricles. The coronary arteries were somewhat narrowed by numerous atheromatous plaques, but nowhere was there an occluding lesion of a coronary artery. The myocardium showed patchy fibrosis.

The lungs showed moderate edema and marked hypostatic congestion. There were two small, white, firm, subpleural nodules near the hilum of the left lung; microscopically, these proved to be old infarcts in an advanced state of healing.

The liver weighed 1,390 grams, and presented gross and microscopic features of chronic passive congestion and fatty metamorphosis.

There was a large, partially organized thrombus in the aorta, extending from just below the celiac artery to the bifurcation of the aorta, and into both common iliac arteries to their bifurcations. The thrombus was firmly attached to the posterior wall of the aorta and did not occlude the lumen entirely, so that the mesenteric arteries presumably had an adequate blood supply. The thrombus reached into both renal arteries, apparently occluding them.

The right kidney weighed 250 grams; the left, 150 grams. The perirenal fat on both sides contained patches of fibrous tissue which was firmly adherent to the renal capsules. The surface of each kidney presented a mosaic appearance; there were sharply demarcated areas of bluish-red, yellow, and bright red discoloration. On cut section, very little normal tissue was seen in either kidney. The pelves and ureters presented a few petechiae. Microscopic sections of the kidneys showed large areas of coagulation necrosis, separated from the adjacent parenchyma by wide, irregular zones of granulation tissue. In the necrotic areas there were large blood vessels containing partially organized thrombi which were attached to the intima. The adjacent nonnecrotic parenchyma appeared edematous, and contained a few scattered hyalinized glomeruli. There were small, scattered, loose collections of lymphocytes. The large and medium-sized arteries showed uniform thickening of their walls.

The brain weighed 1,550 grams. The subarachnoid spaces were obliterated; the gyri were widened and the sulci narrowed. Microscopic sections of the brain showed marked edema. Sections of the brain prepared in xanthidrol solution showed the deposition of an abundant amount of xanthidrol urea. (This test is used frequently in cases of suspected uremia to show the high urea content of the tissues.)

CASE 3. Rheumatic Mitral Disease, Hypertensive Arteriosclerotic Heart Disease, Atrial Fibrillation and Thrombosis, and Embolism at the Bifurcation of the Aorta and Secondary Thrombosis. Congestive Heart Failure.—Mrs. K. H., No. 29858, a 57-year-old housewife, was admitted to the surgical service of the John Sealy Hospital. She was discharged June 25, 1942. She had had nausea and pain in the lower abdominal midline scar region, and had had no bowel movement for three days. At that time she was given Wangensteen suction treatment. She began to have bowel movements, and had one or two every day thereafter. However, nausea persisted.

She was readmitted to the hospital July 4, 1942 with the complaint of pain, coldness, and numbness in the legs. Five days prior to admission, on June 29, she had developed a sudden severe pain in the right calf. This came on about 4 o'clock in the afternoon, when she was walking from the bathroom. This pain was continuous in character and persisted until about noon the next day, when she had another severe pain, this time in the left calf. The pain in the right calf persisted, but was less severe. After that the patient had almost continuous pain in the calves of the legs. The feet had felt cold for four days, and for two days numbness had been noted, especially on the right.

She gave a history of having had dyspnea on exertion, such as going up and down stairs, for three weeks. She had no nocturnal dyspnea, precordial pain, or palpitation. Two weeks before admission nausea had begun, and she also had pain which was made worse by bending the body in the upper lumbar region. She had noticed swelling of her feet.

Physical examination on admission revealed a very obese, middle-aged white woman who was moderately dyspneic. She was alert and cooperative. She was lying flat on her back. Her left eyeball was missing. The right pupil was constricted, but the patient had had morphine previously. The heart was slightly enlarged to the left. The rhythm was grossly irregular. The rate was 90. There were no thrills, and no murmurs were heard. The blood pressure was 200/100. Examination of the lungs revealed a few fine moist râles at the right base and also at the left base anterolaterally.

The abdomen was protuberant. A ventral hernia was present in an operative scar in the lower midline. The liver was down 3 or 4 fingerbreadths below the right costal margin, and there was tenderness in the right costovertebral angle.

Examination of the extremities revealed that the skin of the thighs was cool, and that the legs and feet were cold. There was slight cyanosis of the feet and nail beds. The deep reflexes were decreased. No pulsation could be felt in the dorsalis pedis, posterior tibial, popliteal, or femoral arteries bilaterally. Oscilometric studies revealed no pulsation in the left or right thigh or in the lower part of the legs. The venous pressure was 17.5 cm. of saline. The circulation time was 15 seconds with magnesium sulfate and 25 seconds with ether.

Electrocardiograms revealed auricular fibrillation, with a rapid ventricular rate and definite evidence of myocardial damage.

Urinalysis revealed no significant abnormalities. The blood studies showed no anemia, but a slight polymorphonuclear leucocytosis. The nonprotein nitrogen was 40 mg. per cent, the urea nitrogen, 18.8 mg. per cent, the uric acid, 4.5 mg. per cent, and the creatinine, 0.91 mg. per cent.

The patient's course in the hospital was uneventful. She was kept at rest in bed, and given morphine to control the pain. She was given 3 grains of digitalis twice for one day, and then 3 grains daily.

On July 6 the blood pressure was 180/68. She refused food all day and was unable to void. Five hundred twenty-five c.c. of dark urine were obtained by catheterization. No pulsation could be felt in any of the arteries of the lower extremities, and fecal material obtained by digital examination of the rectum was strongly positive for blood. It was felt that this patient also had mesenteric embolism and infarction.

On July 8 the patient appeared much worse, and cried out almost constantly. The blood pressure was 195/108. The urine output was only 150 c.c. that day. The pulse rate was 70. On July 9, the patient was in about the same condition. On July 10 she was reported to have turned over and fallen out of bed at 6 o'clock in the morning. She was put back in bed and soon after that she was cyanotic, dyspneic, clammy, and perspiring freely. She was given $\frac{1}{6}$ grain of morphine. No pulse could be felt, and the blood pressure could not be measured. She was restless,

complained of pain in the abdomen, legs, and head, and was groaning. She died approximately an hour after she fell out of bed.

Summary of Pathologic Changes (Autopsy No. 5672).—On external examination there was little of significance except that the right leg appeared to be of slightly greater diameter than the left. Opening of the body cavities revealed many fibrous adhesions in the pelvis and about the gall bladder and splenic regions.

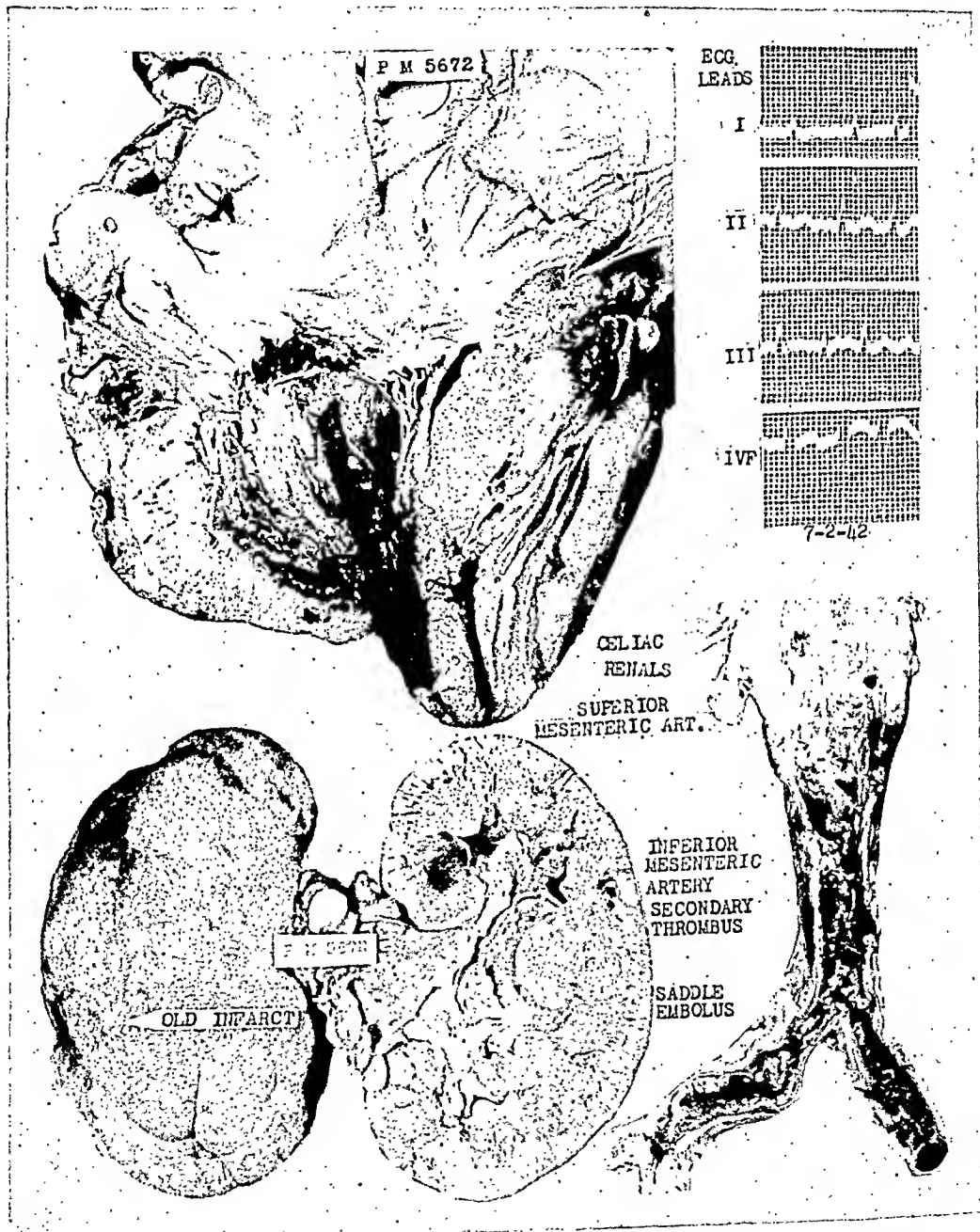


Fig. 3.—Case 3. Mrs. K. H., J. S. Hospital, No. 29858; Post Mortem, No. 5672.
 Right upper: Electrocardiograms showing atrial fibrillation and low voltage.
 Left upper: Aorta, stenosed, fibrosed mitral valve, and left atrium opened. The mural thrombi were lost in the dissection.
 Left lower: The infarcted left kidney.
 Right lower: The atheromatous aorta with the thrombus extending from 5 cm. above the bifurcation of the aorta into the common iliacs.

The heart weighed 600 grams (Fig. 3). There was an abundance of epicardial fat. The myocardium was dark, reddish-brown, and soft and flabby. The left atrium was dilated, its wall and endocardium were thickened, and thrombotic masses were present. All chambers of the heart contained numerous small, firm, whitish thrombi, attached to the endocardial surfaces. The left ventricular wall was 17 mm. thick; the right, 6 mm. The mitral valve leaflets were thickened and adherent to each other, causing moderate stenosis of the mitral orifice. These leaflets were about 0.5 mm. thick along their free edges. At the line of closure on the atrial surface the endocardium was eroded, and a very scanty amount of thrombus clung rather firmly to the small ulcerated area. Microscopic sections through this lesion showed that the vegetation consisted of fibrin and platelets, with scattered leucocytes, but no bacteria. The coronary ostia were slightly narrowed and not distensible. There was slight atherosclerosis of the coronary arteries, but no occlusion was seen.

The aorta showed a marked degree of atherosclerosis. The terminal 4 cm. of aorta contained a complete ring of calcareous deposits which extended slightly into the common iliacs. A thrombus beginning 2 cm. below the ostia of the renal arteries occluded the aorta beyond the bifurcation extending into the common iliacs and for a short distance into the external iliac arteries. In the aorta it was adherent posteriorly, and it was slightly retracted from the wall and free in the iliac vessels. The renal arteries, superior and inferior mesenteric arteries, and celiac axis were patent. The splenic artery was tortuous, had rigid walls, and contained a soft, dark red thrombus throughout its length.

The right lung weighed 550 grams. Along the posterior border of the upper lobe there were several hemorrhagic infarcts, the largest of which measured 4 cm. in its greatest dimension. Two smaller infarcts were seen on the lateral surface of the lower lobe. The left lung weighed 350 grams and appeared to be normal.

At the junction of the esophagus with the cardia, there was a small globular tumor mass in the muscle coat, measuring 7 mm. in diameter. Microscopically this proved to be a leiomyoma. Otherwise, the alimentary tract was normal. The liver weighed 2,100 grams. It showed a slight nutmeg appearance. Microscopically, passive congestion was evident, and, in addition, there were scattered, small areas of focal necrosis in the liver lobules. The gall bladder contained a spherical calculus 1 cm. in diameter. The pancreas showed a marked degree of fatty infiltration.

The spleen weighed 250 grams. At the upper pole it presented a large pale infarct.

The right kidney weighed 250 grams; the left, 170 grams. Both kidneys showed a moderate degree of nephrosclerosis of the benign type. Each kidney showed a few pale infarcts. The internal genitalia were absent. The brain weighed 1,250 grams. There were some small deposits of bony tissue in the dura mater along the sagittal sinus. There was atrophy of the frontal lobes of the cerebrum. Cross sectioning of the brain revealed considerable congestion of the white matter. The basal vessels of the brain showed moderate sclerosis.

CASE 4. Rheumatic Mitral Stenosis, With Atrial Fibrillation, and Intermittent Claudication Due to a Saddle Embolus at the Bifurcation of the Aorta. Cerebral Embolism.—Mrs. S. B., No. 68701, a 40-year-old Viennese refugee, had been diagnosed as having rheumatic mitral stenosis and insufficiency, with congestive failure, in 1938. She presented herself Aug. 20, 1941, complaining of a feeling of heaviness of the left leg, coolness, numbness, and tingling and yellow coloration of the feet, with purple toes on the dependent left foot. Two days previously, while walking about the house, she had had a sudden attack of pain in the calf of her left leg which radiated anteriorly. The left foot felt numb and was cold and blanched. She had some tingling sensation on the medial side of the foot. She went to bed and massaged the part, and soon the color reappeared, but the pain

persisted. Pallor returned two or three times, and each time friction would bring the color back. The foot continued to be cold and numb. After bathing the foot in warm salt water that night, the pain seemed to disappear. She got up and walked again, and after about a block she had the sharp pain in the right leg along the margin of the tibia into the foot. She again went to bed and the pain disappeared, but returned every time she tried to walk. One week preceding the pain in her left foot, she had had a cold with cough and fever, and had developed an irregularity of her heart.

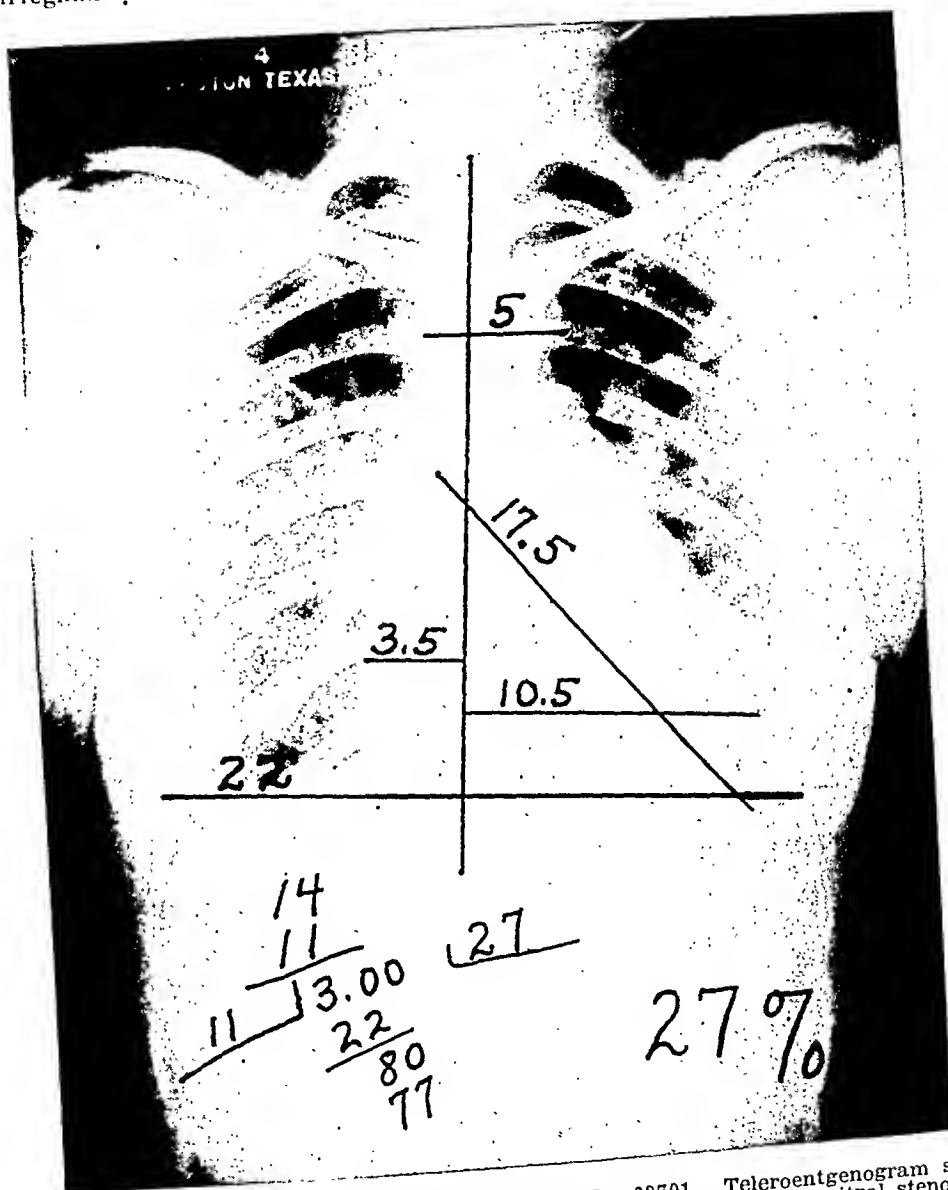
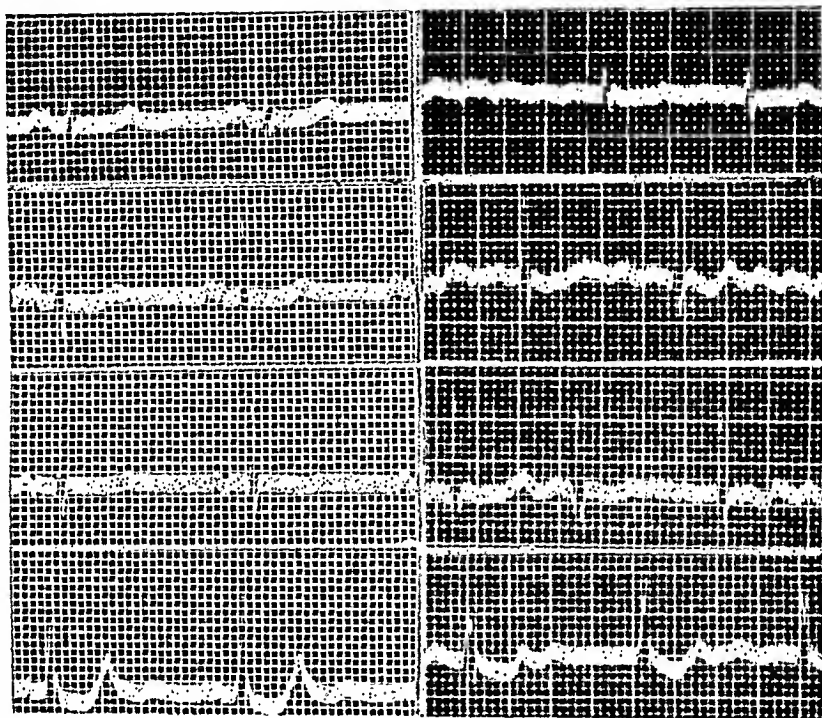


Fig. 4A.—Case 4. Mrs. S. B., J. S. Hospital, No. 68701. Teleroentgenogram showing the characteristic straight left ventricular border of rheumatic mitral stenosis.

Physical examination showed cyanosis and evidences of chronic rheumatic heart disease, with high-grade mitral stenosis. Her heart was enlarged. There were systolic and diastolic thrills over the apex and a diastolic pulmonary shock. The pulmonary second sound was accentuated. There were a loud apical systolic murmur, transmitted to the apex, and a short diastolic murmur. The first apical sound was sharp in spite of the murmur. The heart was somewhat overactive. The rate

was about 110. The rhythm was absolutely irregular. Electrocardiograms showed atrial fibrillation. The blood pressure was 160/100. There was some pulse deficit. The abdomen was protuberant. Examination of the lungs showed râles at the bases. The liver was 1 to 2 fingerbreadths below the right costal margin, and the spleen was palpable.

The extremities showed conspicuous abnormalities. The left foot was cooler than the right. The left big toe was slightly cyanotic and mottled. The dorsalis pedis, popliteal, and femoral pulsations could not be felt on the left, and were barely palpable on the right. There was slight tenderness in the calf of the left leg. The skin temperatures were reduced markedly on the left, and moderately over the right, leg. The oscillometric indices were practically zero in both the thighs and lower part of the legs.



Oct. 15, 1940.

Jan. 9, 1942.

Fig. 4B.—Case 4. Electrocardiograms, from above downward, leads I, II, III, and IV, showing, Oct. 15, 1940, characteristic, broad, notched, diphasic P waves of atrial hypertrophy and tendency to right axis deviation; Jan. 9, 1942, atrial fibrillation.

The patient's course in the hospital was eventful. Paroxysmal attacks of pain recurred in the left leg, and then in the right leg. Cramping pains recurred in the lower abdomen and flanks, and were followed by general tenderness. The edge of the liver and spleen became palpable. She had dyspnea and precordial pain occasionally.

Antispasmodics, postural exercises, and pavaex therapy of the left leg were kept up, even though she had much pain in the leg after the exercises and after the intermittent negative pressure, but the skin of the left leg became warmer. She was discharged improved on Oct. 18, 1941.

She was readmitted Jan. 2, 1942 with an attack of abdominal pain, nausea, and vomiting that was followed by pains in her right leg, with the appearance of pallor and yellowness. The toes on the right foot began to feel peculiar, and a cold wave passed over the plantar surface of the right foot to the heel. Knifelike

pain radiated through to the sole of the right foot, and excruciating, gnawing, constant pain was felt in the right groin. Conspicuous pallor, hyperesthesia with coldness, and absence of peripheral pulses were noted in both legs. Oseillometric studies showed maximum indices of 1 in the right thigh, $1\frac{1}{4}$ in the left thigh, $\frac{3}{4}$ in the right leg, and 1 in the left leg. Abdominal cramps, nausea, and vomiting recurred.* She had attacks of flushing, with burning of the face, neck, arms, and

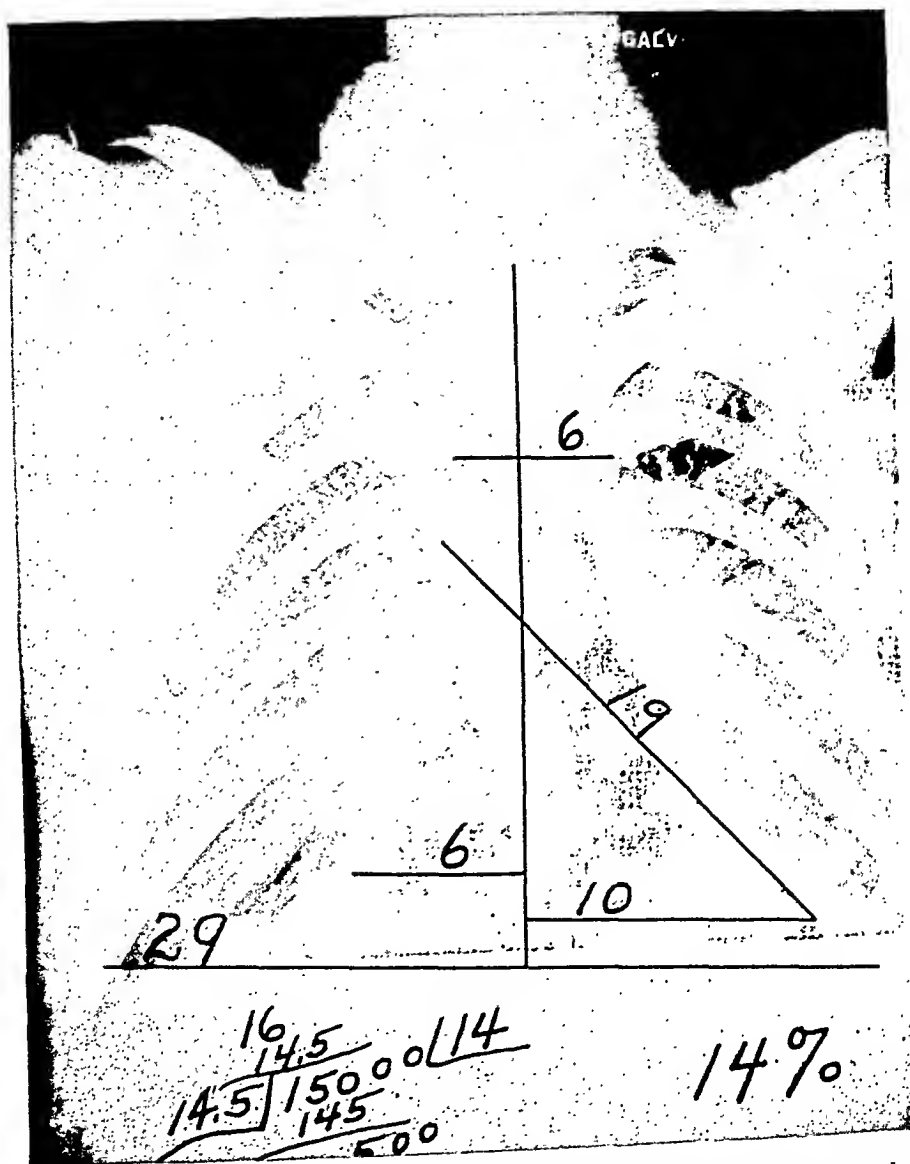
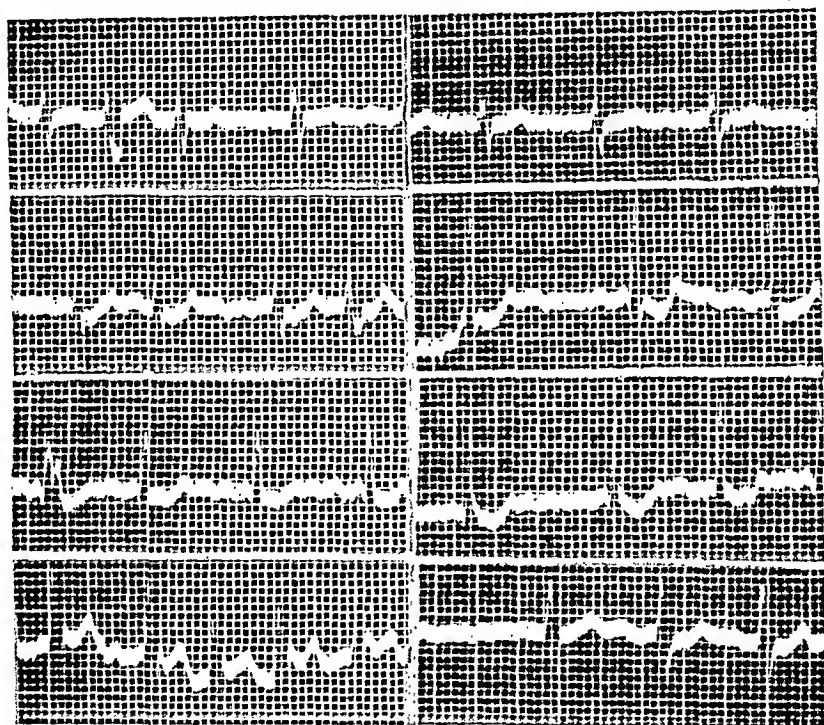


Fig. 5A.—Case 5. C. L. T., J. S. Hospital, No. 75690. Teleroentgenogram showing some bulging in the region of the left atrium, considerable bulging in the right atrium, and congestion in the lung typical of rheumatic mitral stenosis.

hands. The symptoms slowly decreased under conservative medical treatment with a heat eradle, postural exercises, and pavaex therapy. Some paresthesias persisted. On March 20, 1942, she had a syncopal attack, with respiratory standstill. She was partially revived by artificial respiration, but never became conscious again. Shortly before death she had Cheyne-Stokes respiration and the cold grayness of shock. No autopsy was done.

A diagnosis of saddle embolus at the bifurcation of the aorta and terminal cerebral embolism seemed warranted.

CASE 5. *Rheumatic Mitral Stenosis, With Chronic Atrial Fibrillation, Temporary Paraplegia, and a Saddle Embolus at the Bifurcation of the Aorta. Cerebral Embolism and Recovery.*—C. L. T., No. 75690, an insurance salesman, aged 48 years, had had rheumatic heart disease with atrial fibrillation for at least seven or eight years. Early in February, 1942, he contracted mumps, and developed orchitis, which sapped his strength. He stopped the daily use of digitalis which he had carried on for years. On April 2, 1942, he contracted an acute respiratory infection. During the night of April 7, he was awakened by agonizing pain which was sharp and localized behind the right knee. A few hours later he had a similar pain behind the left knee. Both legs became pale and felt very cold. He seemed paralyzed. He had fleeting pains in the abdomen and in the precordium.



April 29, 1942.

May 18, 1942.

Fig. 5B.—Case 5. Electrocardiograms, from above downward, leads I, II, III, and IV F, showing right axis deviation and atrial fibrillation characteristic of advanced rheumatic heart disease.

Physical examination showed a high-grade, uncontrolled atrial fibrillation and the signs of cardiac dilatation and mitral disease. The heart rate was 144, and the blood pressure, 128/80. Marked pallor was noted in both legs, particularly when they were elevated. The skin temperatures were lowered above the knee. The skin of the right leg was cooler than that of the left, and the coolness extended slightly higher. The femoral pulse was not definitely palpable on the right and could barely be felt on the left. The popliteal, dorsalis pedis, and posterior tibial pulses could not be felt definitely on either side. The legs, particularly the right, blanched instantly when elevated and became flushed and slightly cyanosed when held dependent. The subsequent return of color when the legs were horizontal was slow.

The patient was treated with hot and cold applications, whiskey, passive movements, passive vascular exercises, and digitalis. He gradually regained ability to

move his legs, but continued to have attacks of sharp pain, particularly in the right leg.

On April 4, 1942, he was found lying in bed in a semicomatose state, mumbling incoherently; his face was drawn up to the right, and the right arm was limp. In a few days he regained control of the arm and the facial muscles, but he remained mentally confused. He was given 1,000 c.c. of saline by hypodermoclysis. The atrial fibrillation was brought under control with digitalis. His heart rate was reduced to 70. His mental condition gradually cleared under conservative treatment. The pains in the legs decreased and the skin became slightly warmer. He was gradually gotten up in a wheel chair and later allowed to use crutches. One month after his cerebral accident he was discharged much improved.

Diagnosis.—Rheumatic mitral stenosis, atrial fibrillation, saddle embolus at the bifurcation of the aorta, and cerebral embolism.

SUMMARY OF DATA AND CONCLUSIONS

The study of our five cases and of the literature emphasized several interesting clinical diagnostic points. Patients with coronary occlusion and myocardial infarction, and those with rheumatic mitral disease and auricular fibrillation or verrucous endocarditis are candidates for saddle embolism. The bifurcation of the aorta, iliaes, or other great arteries are not uncommon sites for the lodgment of relatively large emboli. The secondary aortic thromboses that follow in atheromatous aortae are most serious and fatal complicating processes.

The occurrence of abdominal cramps should lead one to suspect movement of the emboli down the aorta in predisposed patients. Such symptoms might well be considered significant and premonitory.

Sudden sharp pains in one leg and then in the other, followed by paresthesias, coldness, blanching, lowered skin temperatures, and absent or greatly decreased femoral pulses should lead one to suspect lodgment of an embolus at the bifurcation of the aorta. Oscillometric studies are confirmatory of the absence of pulsations.

The clinical pattern of saddle embolism has been quite clearly delineated. When the embolus is small and the obstruction incomplete, a much less dramatic and less clear-cut clinical picture is presented. It is surprising how benign the condition sometimes seems to be, even after a rather stormy beginning.

Papaverine hydrochloride in a dose of 0.032 Gm. ($\frac{1}{8}$ grain) intravenously should be started as soon after the onset as possible, and repeated as necessary. Morphine is used to control the pain. Whiskey should be administered freely. Passive movements, postural exercises, and pavaex therapy are to be undertaken. Lumbar sympathetic block should be produced as soon as possible to relieve pain and cause maximum peripheral vasodilatation.

In elderly persons the great likelihood of secondary thrombosis in an arteriosclerotic aorta must be kept in mind, and heparinization should be promptly instituted by the intravenous drip method.

Infarction of the kidneys, at times massive from retrograde aortic thrombosis, led to acute uremia in one of our cases. Intermittent

mesenteric obstruction apparently occurred also in the same case. Cerebral embolism may be a further complication.

The length of the time of survival after even complete obstruction and the long postponement of the development of, and the degree of, gangrene are often surprising.

Heparinization, followed by dicoumarol, may, someday, become a routine emergency procedure in the treatment in all cases of massive coronary thrombosis.

The patients with rheumatic heart disease seem to have the best prognosis insofar as saddle embolism is concerned.

Acute saddle embolism of the aorta following trauma in war is likely to occur. In young men this should have a favorable prognosis, especially if the condition is promptly recognized and treated with papaverine, heparin, and passive exercises. If embolectomy should be undertaken, it should be done by an expert vascular surgeon.

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ELECTROCARDIOGRAPHIC CHANGES DURING PNEUMOENCEPHALOGRAPHY

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THE only reports on the electrocardiographic effects of pneumoencephalography are those of Abeles and Schneider,¹ who observed twenty cases, and Ambrosi,² who reported ten additional cases. Abeles and Schneider demonstrated changes in the pacemaking mechanism, including sinus bradycardia, sinus arrhythmia, nodal rhythm, phasic sinus slowing, ventricular extrasystoles, and auricular fibrillation. Ambrosi, who noted only a slight alteration in the heart rate, did not confirm these observations.

In view of this contradiction we believed it advisable to reinvestigate the problem. Theoretically, it seemed that electrocardiographic changes might be expected, inasmuch as the introduction of air into the cranial cavity results in central nervous system irritation. We endeavored to establish a more uniform technique than that employed by previous investigators. Twelve consecutive, unselected patients who were referred to the x-ray department for pneumoencephalograms were studied.

TECHNIQUE

Unless otherwise stated, the patients were prepared by the omission of lunch. One and one-half grains of phenobarbital were given an hour before, and $\frac{1}{75}$ grain of atropine sulfate, hypodermically, a half-hour before the encephalograms were made.

The electrodes were attached and left undisturbed throughout the procedure. After the patient was seated, about 2 c.c. of novocain were introduced into the subcutaneous tissues in the third or fourth lumbar interspace. The needle was inserted into the subarachnoid space, and the first tracing of the three classical leads was recorded before fluid was withdrawn.

Ten cubic centimeters were removed initially, and 5 c.c. of sterile, filtered oxygen were slowly introduced. During the rest of the procedure, equal quantities of fluid were removed and oxygen injected in 5 c.c. interchanges of fluid and gas. By this method sudden increases in the volume of gas in the subarachnoid space were avoided.

Twenty minutes to a half-hour were usually required. In some cases, the procedure was stopped momentarily to take tracings after small quantities of oxygen had been introduced. In all, a complete tracing was taken towards or at the end of the operation. In several instances, follow-up electrocardiograms were made.

Our technique differed from that used by previous investigators in the following details. We employed pure oxygen instead of air. A controlled fluid-gas ratio was maintained, and no wide differences between the amount of fluid removed and gas injected were permitted. The total amount of fluid removed averaged about 80 c.c., whereas the average quantity Abeles and Schneider removed averaged

about 200 c.c. In addition, careful records of the patients' reactions, including pulse rate, blood pressure, temperature, and subjective symptoms, were made before, immediately following, and at periodic intervals after the procedure.

Abeles and Schneider used morphine and scopolamine for premedication. Morphine alone, or in combination with other drugs, has been shown by Bohn⁵ to provide less satisfactory premedication than the phenobarbital and atropine sulfate which we employed.

REPORT OF CASES

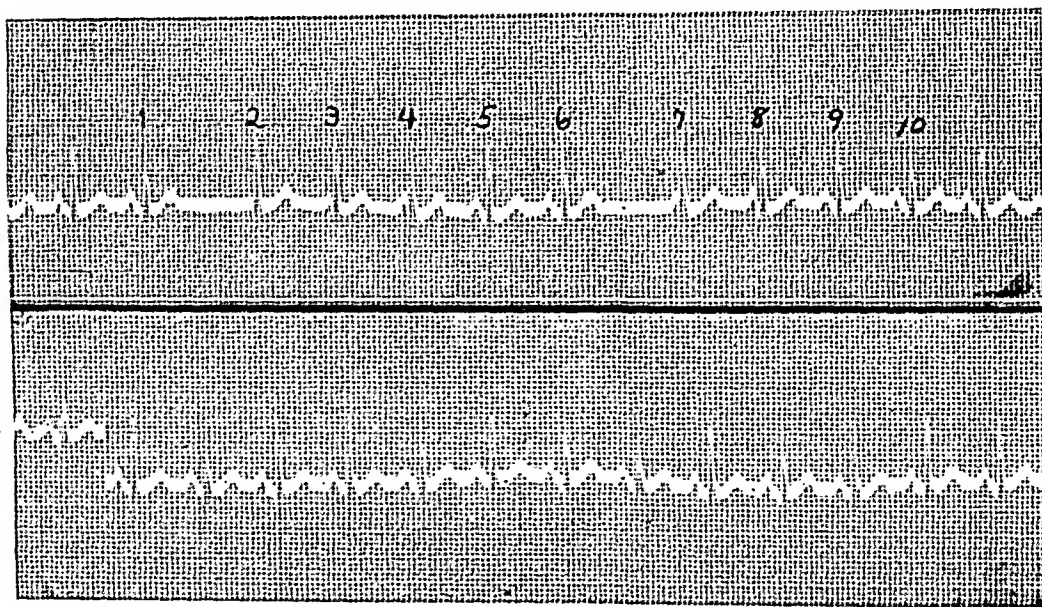
The cases are divided into three groups, according to the degree of alteration in the electrocardiogram. Three of the twelve patients showed marked changes, five showed moderate changes, and four showed only slight variations.

THE THREE CASES IN WHICH THERE WERE MARKED CHANGES

CASE 1.—E. S., a 38-year-old man, had had convulsive seizures and hesitancy of speech for five months. He began to transpose the position of words in sentences before admission.

The positive physical signs included blurring of the nasal margins of the optic discs, absence of the abdominal reflexes, equivocal Babinski and Oppenheim signs on the right side, and a questionable Hoffman sign on the left side. After the encephalograms were made he was discharged with a diagnosis of idiopathic seizures.

A.



B.

Fig. 1A.—Case 1. Lead II, after 20 c.c. of oxygen had been injected, shows dissociation of auricle and ventricle.

Fig. 1B.—Case 1. No irregularity in Lead II after the oxygen injection had been completed.

Before the introduction of oxygen, the electrocardiogram revealed a rate of 125 per minute with a slight tendency towards left axis deviation. After the introduction of 20 c.c. of oxygen the rate slowed to 100, and the pattern of the tracing was abruptly changed. The T wave in Cycle 1 (Fig. 1A) is notched and broadened, probably because a P wave is superimposed. Number 2 is a nodal beat because it is not preceded by a P wave. A P wave probably falls at the peak of

the following T wave. In Cycles 3 and 4 there is dissociation between the auricle and ventricle because the P-R intervals are 0.06 second and 0.08 second, respectively; P falls almost directly into the QRS complexes. Since it normally requires 0.12 second for an impulse to traverse the auricular tissue from the sinoauricular to the auriculoventricular node, we may assume that Cycle 5 shows return to the normal mechanism because P-R measures 0.12 second. In Cycle 6 the P-R interval of 0.14 second is normal.

The same sequence of events follows the main ventricular complex in Cycle 6, namely, a P wave is superimposed on the T wave and there are two nodal beats, followed by a return to normal mechanism. This phenomenon has been called "dissociation and interference" because both the sinoauricular node and the auriculoventricular node are operating independently.⁴ When the sinus impulse arrives at the auriculoventricular node during a refractory period it fails to initiate a ventricular complex.

A tracing taken after the total amount of oxygen had been injected (Fig. 1B) and a follow-up tracing forty-eight hours later showed a slightly slower rate, but no essential variations from the preinjection record.

Comment.—This electrocardiogram showed a marked transient disturbance at the beginning of the injection, at the time of onset of severe headache. There were no progressive changes.

CASE 2.—J. C., a 22-year-old man, complained of seizures involving principally the right hand for the preceding five years. There had been no generalized convulsions and no loss of consciousness. The frequency and severity of the attacks were lessened by the use of phenobarbital. The patient had suffered a head injury at the age of 11 years. He remained in bed for three weeks at that time. When he was 16 years old he was injured by a truck, which struck his head. There were no immediate sequelae.

The positive signs included a rhythmical intention tremor on the right side, and right-sided hyperreflexia and facial weakness. Roentgenograms revealed hypertrophy of the skull bones on the left side. After the pneumoencephalograms were made, he was discharged with a diagnosis of hypoplasia or atrophy of the left cerebral hemisphere (traumatic or congenital).

The electrocardiograms showed many unusual features. The tracing made after insertion of the needle, before oxygen was injected, showed normal sinus rhythm with a rate of 106 per minute. After the injection of 74 c.c. of oxygen (Fig. 2), there was a fall in rate to 80, with marked sinus arrhythmia and many associated abnormalities.

In Lead I, after Cycles 1 and 2, marked slowing of the rate occurs. Cycle 3 is initiated by an abnormally low P wave and a short P-R interval, indicating that the impulse arose, not in the sinus node, but closer to the auriculoventricular node in the auricular musculature. Since the P-R interval in Cycle 3 is about 0.10 second, it is likely that the QRS complex is of nodal origin. Cycle 4 is introduced by an abnormally low, rounded P wave, followed by a normal main ventricular complex. However, the S-T segment, which is isoelectric elsewhere, is bowed upward. The T wave which follows is abnormally round and full. Directly after this T wave there are three flutter waves (rate, 300 per minute) which continue until normal mechanism supervenes in Cycle 5. The tracing from Cycles 4 to 5 may be interpreted as showing auricular flutter, starting in the abnormal P wave of Cycle 4.

In Lead II, marked sinus arrhythmia, with a wandering pacemaker, as manifested by an inverted and diphasic P wave in Cycles 2, 3, and 6, is evident. These occur during periods of marked slowing and indicate that ectopic auricular foci look over the pacemaking mechanism when the sinoauricular node became depressed.

In Lead III, Cycles 1, 2, 3, and 4 show "interference and dissociation" similar to that described in Case 1.

In addition to these disturbances in the conducting mechanism, there are also alterations in the height of the T waves in all leads. Slight alterations in the height of the P waves and a definite elevation in the S-T segment appear in Lead II. A tracing taken twenty-four hours later showed no essential variation from the one taken before the oxygen was introduced.

Comment.—This patient, who was well composed before the procedure, had severe objective and subjective reactions, including nausea, vomiting, sweating, severe headache, and syncope. The electrocardiographic disturbances, which were also very marked, indicated severe vagal depression of the sinus node, followed by a shifting pacemaker, auricular flutter, nodal rhythm, and P- and T-wave changes.

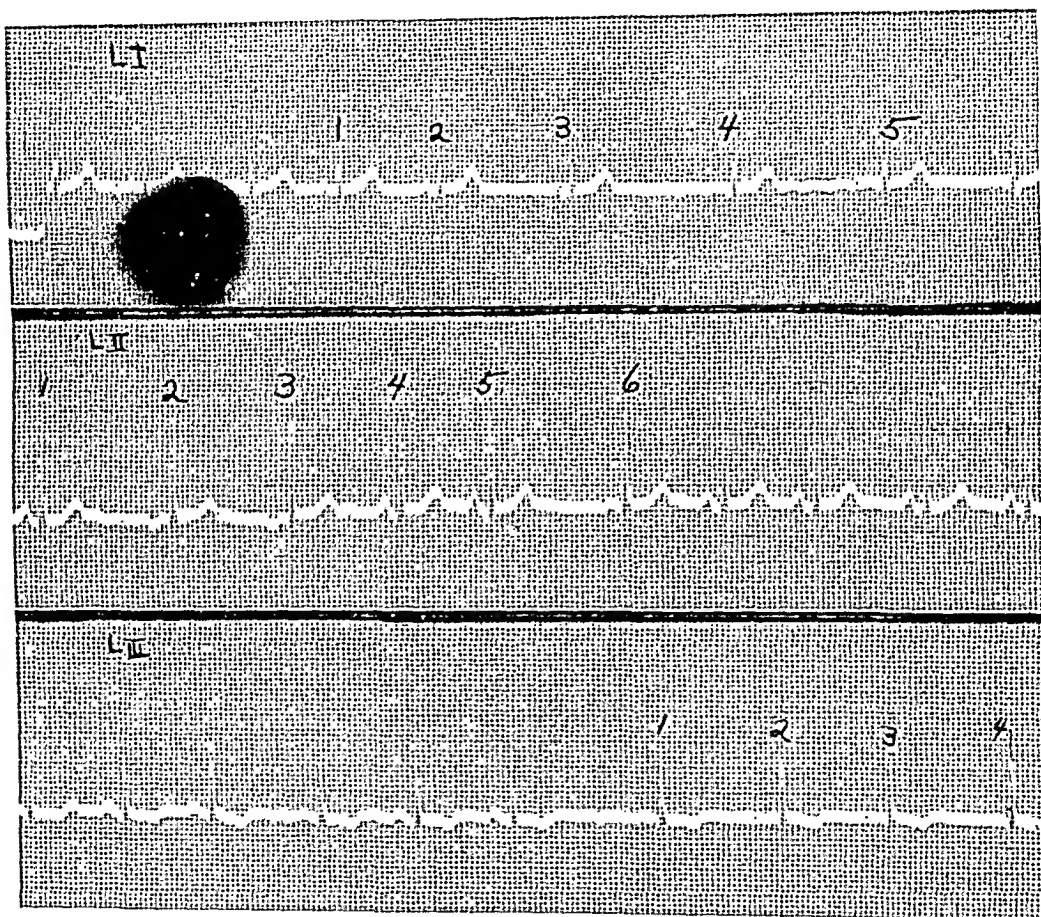


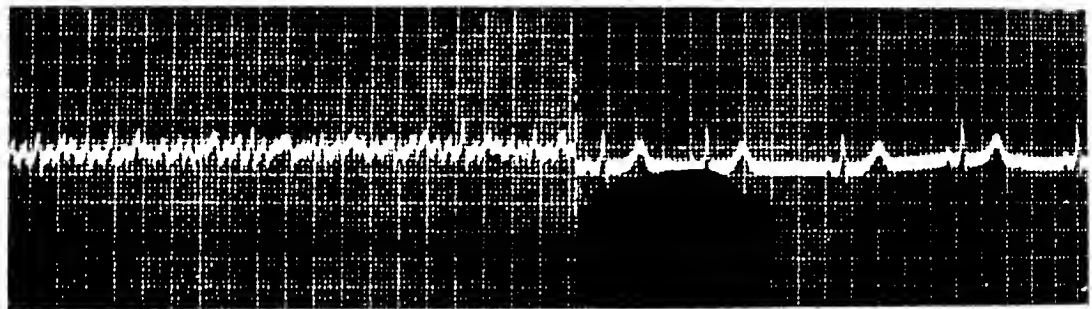
Fig. 2.—Case 2. After 74 c.c. of oxygen had been injected, all three leads show a disturbed pacemaking mechanism, with a wandering pacemaker, auricular flutter, nodal beats, and marked sinus arrhythmia.

CASE 3.—H. K., a 37-year-old woman, complained of numbness of the left hand and progressively severe tremor of the left hand and leg for two months. She had had "muscle weakness" of the left eye for eight years. The patient had had influenza in 1918.

The positive physical signs were atypical mask facies, failure of the left eye to converge, bilateral cogwheel rigidity, and continuous left-sided tremor involving the arm and leg. When she walked there were no associated left arm movements.

After the pneumoencephalograms were made, the patient was discharged with a diagnosis of postencephalitic Parkinson's disease.

The electrocardiographic changes were striking. Before the injection of oxygen the patient had a rapid regular heart rate of 130; a marked somatic tremor permitted us to identify only the main ventricular complexes. After the introduction of 20 c.c. of oxygen (Fig. 3A), there were slowing of the rate to 115 and a slight reduction in the tremor. After the total quantity of oxygen was injected (Fig. 3B), the heart rate fell to about 75, and sinus arrhythmia became evident. In addition, the somatic tremor entirely disappeared, and every portion of the record was clear. The tremor returned after a few hours, and the heart reached its usual rate of between 80 and 90 in twenty-four hours.



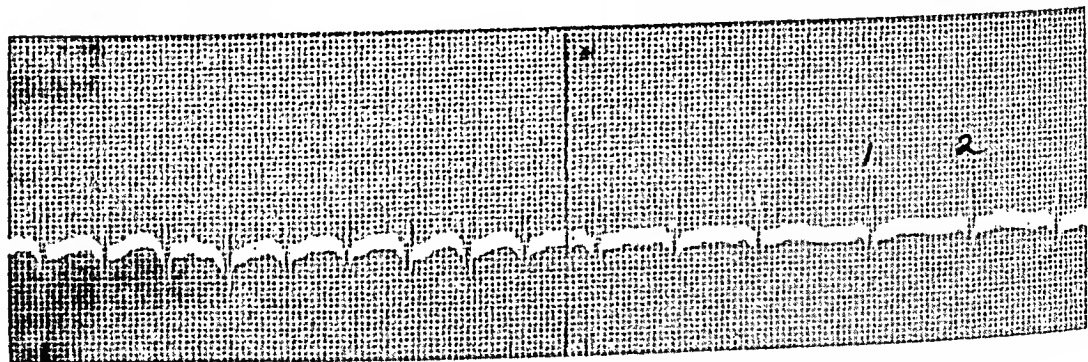
A.

B.

Fig. 3A.—Case 3. After 20 c.c. of oxygen had been injected, marked somatic tremor persisted in this patient with Parkinson's disease. There is a rapid, regular rhythm.

Fig. 3B.—Case 3. After the injection of 110 c.c. of oxygen, the tremor disappears and sinus arrhythmia becomes apparent.

Comment.—The development of marked sinus arrhythmia and a bradycardia which persisted for many hours indicated a prolonged vagal effect. The patient had relief from her tremor for the only time since the beginning of her illness. One would not expect this to result from increased vagal activity because atropine or atropine-like drugs are most beneficial in Parkinson's disease. We know of no satisfactory explanation for this phenomenon. In this instance, too, moderately severe nausea and headache occurred at the same time as the electrocardiographic changes.



A.

B.

Fig. 4A.—Case 4. Lead I, taken with the patient under general ether anesthesia, shows a rate of 160 per minute.

Fig. 4B.—Case 4. After 60 c.c. of oxygen, the heart slows to 110. Sinus arrhythmia and a disturbed pacemaking mechanism are observed. The P-R interval in Cycles 1 and 2 is abnormally short.

THE FIVE CASES IN WHICH THERE WERE MODERATE CHANGES

CASE 4.—T. K., a 9-year-old boy, had had momentary seizures involving the right hand during the preceding eighteen months. Two days before admission the patient had two severe jacksonian seizures.

Physical and laboratory examination showed nothing abnormal.

After encephalograms had been made, the patient was discharged with a diagnosis of idiopathic epilepsy. Pneumoencephalograms were made under general ether anesthesia. The premedication consisted of one grain of phenobarbital the night before, $1\frac{1}{2}$ grains of nembutal two hours before, and $\frac{1}{100}$ grain of atropine sulfate three-quarters of an hour before the procedure.

The electrocardiogram, which was taken after the patient was well anesthetized, and with the needle in situ, revealed a sinus tachycardia of 160; fusion of the P and T waves made most measurements inaccurate. There was marked cyclic alteration in the height and direction of the main ventricular complexes, probably a respiratory effect (Fig. 4A).

After the injection of 6 c.c. of oxygen (Fig. 4B), the rate slowed to 110, and the individual waves could be measured readily. The QRS complexes were taller and did not vary as much in height or direction as in the initial tracing. There was moderate sinus arrhythmia. The P-R intervals in Cycles 1 and 2 in Lead I shorten from 0.14 second to 0.10 second, indicating a wandering pacemaker. A tracing taken seventy-two hours later showed slowing of the heart rate to 80, with slight sinus arrhythmia.

Comment.—Despite general anesthesia and lack of subjective reactions, evidence of vagal stimulation was present in the electrocardiogram.

CASE 5.—J. H., a 55-year-old man, entered with a complaint of dizzy spells for three years and syncopal attacks which had become more severe during the preceding six months.

Examination revealed sclerotic peripheral vessels and questionable pallor of the left optic disc. After pneumoencephalograms had been made, the patient was discharged with a diagnosis of cerebral arteriosclerosis.

A tracing taken two days before the encephalograms were made showed normal sinus rhythm and a rate of 75 per minute. There was left axis deviation, and the T wave was inverted in Lead III. Because of technical difficulties we were unable to obtain a satisfactory tracing immediately before the injection of oxygen. The record made after the injection of 20 c.c. of oxygen showed several changes. The rhythm was normal and the rate was 110 per minute. There was an increase in voltage, particularly in Lead II. In Lead III, the change of the T wave from an inverted to an upright position is unusual. The P waves and T waves in the other leads were higher. In the record taken immediately after the injection of 70 c.c. of oxygen, the T waves had returned to the inverted position and the record resembled more closely the two control tracings. The increased voltage persisted and the P and T waves were elevated, but not as markedly as in the tracing taken after only 20 c.c. had been injected.

Comment.—The most marked electrocardiographic changes occurred early in the procedure, as in Case 1. They were accompanied by a transient period of retching and the onset of headache.

CASE 6.—A. B., a 14-year-old-boy, had had seizures in the right arm for three years. The past history was significant in that the patient was born by breech extraction and had had convulsions early in infancy. At the age of 6 years, he was hit by an automobile and was unconscious for five days.

On examination he showed mental retardation and atrophy of the right lower extremity. The right leg was shorter and smaller than the left. There was marked right-sided hyperreflexia.

Electrocardiographic studies before the injection of oxygen (Fig. 5A) showed sinus tachycardia (125 per minute). A tracing taken after 45 c.c. of oxygen had been injected (Fig. 5B), showed slight reduction in rate (to 110), with definite elevation of the T waves in all leads, including Lead III, in which the T waves were inverted. In addition, the S-T segments in Leads I and II were somewhat depressed. There was also deepening of the S wave in Lead II. In Lead III the P waves were considerably reduced in size.

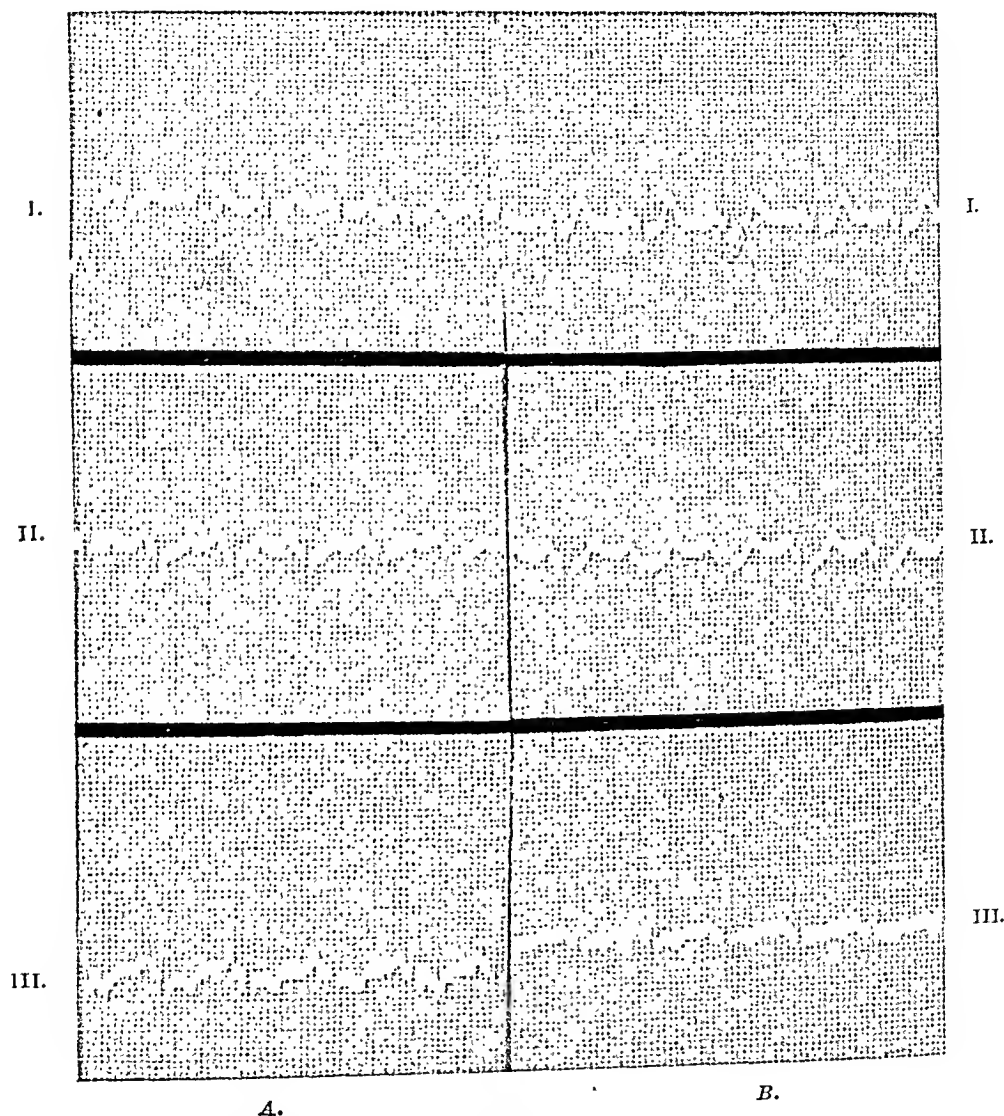


Fig. 5A.—Case 6. Before the injection of oxygen.

Fig. 5B.—Case 6. After 45 c.c. of oxygen had been injected. Elevation of T waves and depression of P waves in all leads, together with an insignificant decrease in rate.

Comment.—This case demonstrated primarily a change in the P and T waves, with no appreciable alteration in the pacemaker. These changes may have been caused by increased vagal activity.

CASE 7.—S. M., an 8-year-old boy, entered the hospital because of dizziness and frontal headache for six months. During an attack he developed pain and a limp in the left leg. Four years previously he had been injured in an automobile accident. A diagnosis of concussion of the brain had been made at that time.

Examination showed a talkative, excitable child. Nystagmus of a congenital nature was present. There were girdle adiposity and a healed right mastoid scar, but no localizing neurologic signs. The patient was discharged with a diagnosis of a right cerebral scar and mild mental deficiency.

Pneumoencephalograms were made under general ether anesthesia.

The electrocardiogram showed normal sinus rhythm, and a rate of 100 before oxygen injection. After the introduction of 80 c.c. of oxygen the rate increased to 110, accompanied by an increase in voltage. In all leads the S-T segment became longer, and the upstroke of the T wave in Leads I and III was more gradual, with an earlier take-off. The T wave in Lead III, which was barely inverted in the initial tracing, was definitely deepened and inverted in the post-operative tracing.

Comment.—This is another case in which the changes were primarily confined to the configuration of the T waves and the S-T segments.

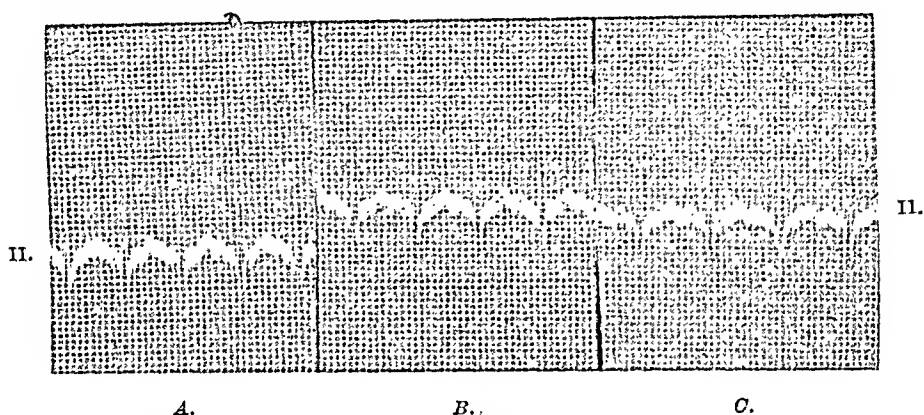


Fig. 6A.—Case 9. Rapid, regular rhythm before the introduction of oxygen.

Fig. 6B.—Case 9. After injection of 20 c.c. of oxygen.

Fig. 6C.—Case 9. Only slight slowing after injection of 75 c.c. of oxygen.

CASE 8.—P. F., a 43-year-old woman, was admitted because of difficulty in walking, weakness of the legs, and frontal headaches for about one year. Shortly before, personality changes, surliness, carelessness, and poor memory had become apparent.

On examination the patient manifested frequent mood changes, poor memory for recent events, a positive Babinski on the left, and slightly slurred speech.

Three days after pneumoencephalograms were made, a right frontal craniotomy was performed and a large portion of a glioblastoma multiforme was removed. The patient expired four days after operation.

A tracing before insertion of the needle was identical with that taken after the needle had been inserted. After 20 c.c. of oxygen were injected, the rate increased from 80 to 100 per minute. Although the patient held herself tensely, a satisfactory second lead tracing was obtained; it showed elevation of the P wave from 3 to 5 mm., with a sharp upstroke and peak. After the injection of 75 c.c. of oxygen, an increase of the P waves in all leads persisted, and moderate elevation of all the T waves appeared. A record taken seventy-two hours later showed little variation from the preoperative control tracing.

Comment.—The patient cooperated very well in the early part of the procedure, but then became very excited, restless, and somewhat irrational. This explains the fact that there was an increase, rather than a decrease in heart rate. It is interesting that, despite this, there were T-wave changes similar in character to those in records in which the heart rate was diminished.

TABLE

CASE	DIAGNOSIS	EKG CHANGES	IMMEDIATE REACTIONS	DELAYED REACTIONS	BLOOD	
					BASAL	P.O.
No. 1 male, 38 E. S.	Convulsive seizures, idiopathic	Rate slows, nodal beats, dissociation and inter- ference of SA and AV nodes	Headache	Backache 1 day, headache 4 days	140/90	130/90
No. 2 male, 22 J. C.	Hypoplasia, left cerebral hemisphere	Rate slows, nodal beats, auricular flutter, sinus arrhythmia, wandering pacemaker, S-T and T- wave elevation	Headache, sweating, pallor, vomiting, syncope	Chills 1 hour, headache 12 hours, backache 24 hours	140/96	138/65
No. 3 female, 37 H. K.	Postenceph- alitic Parkinsonism	Rate slows, sinus arrhyth- mia, disappearance of somatic tremor	Headache, nausea, vomiting	Nausea 24 hours, headache 48 hours	112/70	100/70
No. 4 male, 9 T. K.	Jacksonian seizures, origin unde- termined	Rate slows, sinus arrhyth- mia, wandering pace- maker, increased volt- age	None: pa- tient under general anes- thesia	Headache 48 hours, backache 48 hours		110/70
No. 5 male, 55 J. H.	Cerebral arterio- sclerosis	Rate slows, increased voltage, P and T waves elevated	Headache, nausea, retching	Headache 18 hours	116/80	120/80
No. 6 male, 14 A. B.	Birth injury, left motor cortex	Rate slows, T-wave eleva- tion, S-T segment de- pression, P-wave de- pression	Headache	Chills 1 hour, backache 36 hours, headache 48 hours	110/60	90/55
No. 7 male, 8 S. M.	Cerebral scar, right	Rate accelerates, T-wave and S-T segments alter- ations	None: pa- tient under general anes- thesia	Pain in ears 12 hours		120/90
No. 8 female, 43 P. F.	Glioblastoma multiforme, right frontal area	Rate accelerates, P- and T-wave elevation	Headache, nausea	Restless 48 hours, headache 72 hours	116/70	110/70
No. 9 male, 37 N. G.	Headache due to conversion hysteria	Rate slows slightly, less tendency to left axis deviation	Headache, nausea, retching	Headache 25 hours, backache 24 hours	130/98	120/90
No. 10 male, 30 J. C.	Postconcus- sion syn- drome	Rate slows slightly, slight T-wave elevation	Severe headache	Headache 48 hours	138/84	110/75
No. 11 female, 26 F. R.	Idiopathic convulsive disorder	Rate slows slightly, mini- mal T-wave and S-T segment elevation	Headache, nausea, retching	Chills 15 min., dizziness 24 hours, headache 4 days	100/70	100/70
No. 12 male, 38 E. D.	Cerebral arte- riosclerosis	Rate slows slightly	Headache, sweating	Chills 12 hours, headache 24 hours	140/90	160/130

THE FOUR CASES IN WHICH THERE WERE SLIGHT CHANGES

CASE 9.—N. G., a 37-year-old man, complained of headache for four months, accompanied by faulty memory. Many years before, the patient had had "spastic colitis." The patient was emotionally upset.

Examination revealed an agitated normal man with hyperactive deep reflexes, absent abdominal reflexes, and a slightly enlarged prostate. He showed evidences

I

PRESSURE		PULSE				TEMPERATURE				LUMBAR PUNCTURE		SPINAL FLUID C.C. REMOVED	OXYGEN C.C. INJECTED
										MM. H ₂ O			
4 HR.	24 HR.	BASAL	P.O.	4 HR.	24 HR.	BASAL	P.O.	4 HR.	24 HR.	IMME- DIATE PRES- SURE	FINAL PRES- SURE		
150/100	130/100	80 to 90	80	120	80	98 to 99	98.6	101.2	98.6	185	115	90	80
130/80	140/98	70 to 90	74	90	84	98 to 100	98.6	101	99	290	275	77	74
	86/72	80 to 90	68	72	88	98.6 to 100	98.6	99.8	100	130	70	115	110
112/70		70 to 80	80	116	88	97 to 99.2	98	99.2	99.2	---	---	70	60
130/80	124/80	60 to 80	70	90	72	98 to 99.2	99.4	100.8	99.8	140	125	75	70
110/60	114/64	80 to 90	72	80	80	98 to 99	99	100.6	98.6	180	120	63	61
105/75		88 to 100	92	120	88	98 to 100	97.8	101	98.6	---	---	85	80
140/90	110/70	70 to 90	100	64	80	98 to 99.9	98.6	100	98.6	170	90	80	75
140/80	124/88	75 to 120	118	100	118	99 to 99.8	99.2	100.4	99.8	170	95	80	75
120/74	126/76	80 to 90	102	90	90	98 to 99.6	100	100.2	99	180	130	45	40
105/80	90/60	70 to 90	92	90	90	98 to 99	97.4	100	99.2	120	68	80	75
150/110	150/130	70 to 90	120	120	90	98 to 100	99	100	99	110	60	76	75

of vasomotor instability. After pneumoencephalograms had been made, the patient was discharged with a diagnosis of headache caused by conversion hysteria.

The electrocardiographic changes were minimal. A sinus tachycardia of 165 in the initial tracing (Fig. 6A) slowed to 150 after the introduction of 20 c.c. of oxygen (Fig. 6B), and to 135 after 75 c.c. of oxygen were injected (Fig. 6C). The individual waves cannot be well differentiated. In the initial record there was a tendency to left axis deviation. This was diminished in the final tracing.

Comment.—This patient was extremely anxious prior to the procedure. Sympathetic hyperactivity was reflected in the record, which showed only slight slowing and minimal modification during encephalography. He suffered from nausea, retching, and headache, but there was little correlation between these symptoms and the minimal electrocardiographic changes.

CASE 10.—J. C., a 30-year-old man, was admitted to the hospital because of dizziness and headache for one year following a fall. Examination revealed a markedly apprehensive man with a scar over the right temple and tenderness over the lumbar spine.

After encephalograms had been made he was discharged with a diagnosis of postconcussion syndrome.

The electrocardiographic changes were minimal. A tracing, taken after the injection of 10 c.c. of oxygen, revealed no alteration in the tachycardia (140) which was present before the injection. The final tracing, taken after the injection of 40 c.c. of oxygen, showed only slight slowing of the rate (to 130). Lead II, taken after 10 c.c. had been injected, showed slight elevation of the T waves which was not present in the final record.

Comment.—Only 40 c.c. of oxygen were injected. This might account for the slight electrocardiographic changes. It is doubtful, however, whether a larger quantity of oxygen would have caused further changes, because the most marked alterations occurred at the beginning of the injection. This patient was extremely apprehensive. Fear prevented any appreciable alteration in either rate, rhythm, or configuration by producing increased sympathetic activity.

CASE 11.—F. R., a 26-year-old woman, had had convulsive seizures in the left foot two or three times a year for thirteen years, followed by spread to the left arm and right leg. For seven months she had had daily occipital and frontal headaches. The patient had had heart disease since birth.

Examination revealed a pale, thin, apprehensive, cyanotic woman with loud systolic murmurs, an enlarged heart, clubbing of the fingers, and bilateral pes cavus.

The electrocardiographic changes were insignificant. A slight slowing of the rate (from 130, initially, to 110 at the end of the procedure) was observed. A very slight elevation of the T waves and S-T segments appeared in Leads II and III after 25 c.c. of the gas had been injected. Marked right axis deviation and abnormally large P waves in Leads II and III were present in all the tracings. These were ascribed to the congenital cardiac defect.

Comment.—Again, the only measurable changes occurred early in the procedure. Her extreme anxiety was responsible for the initial and persistent tachycardia. No correlation existed between the minimal electrocardiographic changes and the moderately severe retching, nausea, and vomiting.

CASE 12.—E. D., a 38-year-old man, had a severe dizzy spell three weeks before admission. Three years previously he had had a transient hemiplegia which cleared completely within forty-eight hours.

Examination revealed mental retardation, retinal arteriosclerosis, and mild hypertension. The pneumoencephalogram showed definite dilatation of the sulci, and he was discharged with a diagnosis of encephalomalacia secondary to arteriosclerosis.

The electrocardiograms showed little alteration. An initial tachycardia of 140 slowed to 130 at the end of the procedure. Low voltage was present in all leads in the preoperative tracings, as well as in those taken during and after the procedure. Very slight elevation of the T wave in Lead II was observed after the injection of 50 c.c. of oxygen.

Comment.—This man was worried for two days before the encephalograms were made. Other than headache, there were no symptoms. The tachycardia was a reflection of his anxiety. The minimal alterations in the electrocardiogram may have been caused by sympathetic overactivity.

DISCUSSION

In eight of our twelve cases, appreciable electrocardiographic changes occurred during pneumoencephalography. Abeles and Schneider reported an incidence of 75 per cent in their twenty cases. Our observations do not confirm those of Ambrosi, who reported only slight alterations in the heart rate. We found alterations which varied in type and degree in all our cases. They can be divided into two general categories: those concerned with the pacemaking mechanism, and those which, for lack of a better name, may be called wave changes. Both types may occur in the same patient.

In ten cases in the first group there were changes which varied from a slight slowing of rate to sinus arrhythmias, nodal beats, auriculoventricular dissociation and interference, wandering pacemaker, and auricular flutter.

In eight cases in the second group there were slight to marked alterations in the P and T waves and the S-T segments. Variations in the height and direction of the QRS complexes occurred in two cases. These two types of alterations have no direct relationship to each other. In some cases only slight wave changes appeared when there was a marked pacemaker disturbance. In other cases the converse was true.

The electrocardiographic changes in several cases were most marked at the beginning of the procedure. In others, the changes began immediately upon the introduction of the gas and progressed throughout the procedure. The changes in the pacemaking mechanism were caused by vagal activity. The rapidity with which these alterations were initiated suggested a central mechanism. It is possible that the wave changes also were of vagal origin.

The electrocardiographic changes could not be correlated with the other side reactions in degree. Nausea, headache, and similar complaints commenced at the same time as the electrocardiographic alterations. In three patients with minimal electrocardiographic changes there were severe subjective symptoms (Cases 9, 11, and 12). Two other patients with marked or moderate electrocardiographic variations had minimal symptoms (Cases 1 and 6). From this lack of correlation one may conclude that the introduction of oxygen into the subarachnoid space stimulates several centers simultaneously, but not to the same extent. It is our belief that the cardiac changes are caused principally by central vagal stimulation, whereas the other side-reactions are, for the most part, brought about in other ways.

Vagal stimulation in itself may be responsible for side-effects. In the only case in which syncope occurred, evidence of more powerful vagal

stimulation was found in the electrocardiogram than in any other tracing. There can be little doubt that, in this instance, the central vagal mechanism was responsible for the collapse. The syncope in this case was different from the reflex vasovagal or vagovagal type, in that the stimulation reached the central nervous system directly.

In those cases in which the changes were minimal, the patients were most apprehensive and excitable, and showed marked tachycardia. The dose of $\frac{1}{75}$ grain of atropine, which was given before making the encephalograms, was well below that required to cause alteration in the heart rate.³ It is reasonable to assume, therefore, that in these instances the psychic disturbance caused a marked sympathetic outflow which prevented any abnormal vagal stimulation from altering the pacemaker mechanism or initiating conductive changes in the heart itself. It would follow, then, that larger doses of atropine might be used for the normal adult as routine premedication. In addition, it would seem advisable to reinforce this with one of the sympathicomimetic drugs.

SUMMARY

Electrocardiographic changes indicative of increased vagal activity occur during encephalography.

The authors wish to express their thanks to Dr. L. M. Davidoff and Dr. M. G. Wasch for their cooperation and interest.

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STUDIES OF THE VARIATION IN CIRCULATORY AND RESPIRATORY RESPONSES TO CAROTID SINUS STIMULATION IN MAN

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IT IS now nearly a century and a half since Parry¹ noticed that pressure on the neck along the course of the carotid arteries might cause slowing of the heart, but only lately has the nature of the mechanism become clear. Prior to recent work it was generally regarded as due to stimulation of the vagus nerve,^{2, 3} and came to be known as "Vagus-druckversuch" or "vagus pressure test." In 1900, Pagano⁴ and Siciliano⁵ showed, however, that although the cardiac slowing was mediated through the vagus, it was primarily dependent upon a reflex from the carotid arteries, and Sollmann and Brown,⁶ in 1912, clearly demonstrated that traction on the carotid arteries in the absence of stimulation of the vagus nerve produced a fall in arterial pressure as well as slowing of the heart. Hering's^{7, 8, 9} painstaking physiologic and anatomic studies (1923 to 1927) on the pathways of the nervous impulses first served to bring general recognition to the reflex nature of the phenomenon. Through the work of Hering's associate, Koch,^{10, 11} and Heymans and his co-workers,^{12, 13, 14} De Castro,¹⁵ and Sunder-Plassmann,¹⁶ a clearer definition of the mechanism of the carotid sinus and its pathways came about.

In 1933 and 1935, Weiss and Baker¹⁷ and Ferris, Capps, and Weiss¹⁸ reported instances of syncope and convulsions in persons in whom it was easy to reproduce attacks by slight pressure upon the carotid sinus. Hering⁸ had suggested that such a response might account for certain instances of syncope and convulsions in man. Weiss and his co-workers distinguished three types of syncope as a result of carotid sinus stimulation. Usually two or more varieties occurred simultaneously. The first, in which syncope was accompanied by marked slowing of the heart rate or asystole, and a consequent fall in arterial pressure, was designated the "vagal type;" the second, in which a marked fall in arterial pressure occurred without significant slowing of the heart, the "depressor type"; and the third, in which there was syncope without either slowing of the heart or fall in arterial pressure, the "cerebral type." A response similar to the "cerebral type" was reported at about the same time by Danielopolu,¹⁹ who believed that hypersensitivity of the

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TABLE I
CIRCULATORY CHANGES IN PATIENTS WITH CAROTID SINUS SYNCOPE

CASE	AGE	ARTERIAL PRESSURE		PULSE RATE		TYPE OF RESPONSE			SYNCOPE AND/OR CONVULSIONS	DIAGNOSIS
		RESTING	DURING STIM.	RESTING	DURING STIM.	V*	D*	C*		
1. J. M.	53	R 240-250	130	90	5-7 sec. asystole	+	-	-	yes	General arteriosclerosis, arterial hypertension
		L 240-250	150	90	36	+	-	-	no	
2. A. M.	46	R 170	120	84	5½ sec. asystole	+	-	-	yes	Cirrhosis of liver
		L 90	60							
3. R. P.	50	L Arterial tracing not obtained								Pulmonary tuberculosis postoperative bilateral lumbar sympathectomy for frostbite of both feet
		R 170	90	96	36 with 3 sec. asystole	+	-	-	yes	
4. E. B.	55	L 150	110	80	48	+	+	-	no	Tabes dorsalis, arterial hypertension
		L 90	60							
5. J. K.	56	R 210-220	95	108	24	+	+	-	yes	Arterial hypertension, general arteriosclerosis, right hemiplegia
		L 100-110	40	108	40	+	+	-	no	
		R 180	100	60	7 sec. asystole	+	+	?	yes	
		L 90	50	60	14 sec. asystole	+	+	-	yes	

All patients listed are males.

*V—vagal, D—depressor, C—cerebral.

6 C. K.	69	R $\frac{180-190}{90}$ L $\frac{180-190}{90}$	$\frac{70}{40}$	60	10-13 sec. asystole	+	+	-	yes	General arteriosclerosis, Parkinson's syndrome, arterial hypertension
7. A. S.	60	R $\frac{220}{110}$ L $\frac{220}{110}$	$\frac{140}{70}$	68	48	+	+	-	yes	Tabes dorsalis, arterial hypertension
			$\frac{160}{80}$	68	60	+	+	-	no	
8. W. B.	77	R $\frac{210-220}{110}$ L $\frac{210-220}{110}$	$\frac{110}{50}$	82	32 with 5 sec. asystole	+	+	-	no	General arteriosclerosis, pulmonary fibrosis and emphysema, arterial hypertension
			$\frac{100}{50}$	82	10-15 sec. asystole	+	+	-	yes	
9. F. H.	77	R $\frac{150}{75}$ L $\frac{150}{75}$	$\frac{100}{50}$	84	5 sec. asystole	+	+	-	yes	General arteriosclerosis, arteriosclerotic heart disease, cirrhosis of liver
			$\frac{100}{50}$	84	36	+	+	-	no	
10. C. M.	57	R $\frac{190}{100-110}$ L $\frac{190}{110}$	$\frac{110-130}{60}$	72	36	+	+	-	no	Subacute combined sclerosis, pernicious anemia, arterial hypertension
			$\frac{120}{70}$	80	48 with 3 sec. asystole	+	+	-	yes	
11. J. F.	70	R $\frac{170}{80}$ L $\frac{150}{80}$	$\frac{110}{50}$	72	6 sec. asystole	+	+	-	yes	General arteriosclerosis, right hemiplegia
			$\frac{130}{70}$	60	48	+	+	-	no	
12. E. D.	52	R $\frac{160}{100}$	$\frac{90}{50}$	90	10 sec. asystole	+	+	-	yes	General arteriosclerosis, arterial hypertension, thrombosis left common, external and internal carotid arteries

†Cases 12, 14. Thrombosed left carotid arteries were surgically removed prior to the study. There was no hypersensitivity of the carotid sinus of this side.

TABLE I—CONT'D

CASE	AGE	ARTERIAL PRESSURE		PULSE RATE		TYPE OF RESPONSE			SYNCOPE AND/OR CONVULSIONS	DIAGNOSIS
		RESTING	DURING STIM.	RESTING	DURING STIM.	V*	D*	C*		
13. O. C.	69		170	90	13	+	+	+	yes	Meningovascular syphilis, arterial hypertension
		R $\frac{230-240}{100-110}$	$\frac{60}{150}$	90	60	+	+	+	yes	
		L $\frac{230-240}{100-110}$	$\frac{70}{180}$	96	36	+	+	+	yes	
14.† R. S.	51	R $\frac{300}{140}$	$\frac{75}{180}$							Arterial hypertension, general arteriosclerosis, thrombosis left common, internal and external carotid arteries
15. G. K.	65		80	66	48	+	+	-	no	General arteriosclerosis
		R $\frac{120}{70}$	$\frac{50}{80}$	72	48	+	+	+	yes	
		L $\frac{120}{70}$	$\frac{50}{110}$	102	62 with 3 sec. asystole	+	+	-	no	
16. J. L.	70	R $\frac{200}{90}$	$\frac{50}{180}$	102	84	+	+	+	yes	Arterial hypertension, general arteriosclerosis, right hemiplegia
		L $\frac{200}{90}$	$\frac{80}{190}$	96	36	+	+	-	no	
		R $\frac{260}{110}$	$\frac{100}{260}$	96	96	-	-	+	yes	
17. C. N.	53	L $\frac{260}{110}$								Meningovascular syphilis, arterial hypertension, general arteriosclerosis

carotid sinus played an important role in the cause of convulsions in epileptics.

Because of the difficulty in following changes in arterial pressure and pulse rate continuously by the usual technique during the brief period in which the reactions caused by pressure upon the carotid sinus occur, the existence of the so-called cerebral type has been in doubt. Since methods of recording arterial pressure and pulse rate continuously by direct intra-arterial measurements have recently become available,^{20, 21} a restudy of the relationships, in point of time, between changes in arterial pressure, pulse rate, venous pressure, respiration, and the onset of syncope and convulsions was believed warranted.

One hundred persons were examined, twenty-six of whom had a sensitive carotid sinus reflex, in the sense that syncope and convulsions, with or without circulatory changes, occurred promptly with gentle pressure. Of these, seventeen regularly had convulsive seizures on stimulation of the carotid sinus. All of them were men whose ages ranged from 46 to 77 years (Table I). Four women and five men were not sufficiently cooperative for detailed study. Three patients (Cases 11, 12, and 15) gave a history of having experienced spontaneous attacks similar to those produced by pressure on the carotid sinus.

METHODS

The patient was placed in the supine position on a comfortable stretcher, with the arm to be used for arterial puncture extended on a padded board support at an angle of about 70° or 80° to the longitudinal axis of the body. The radial artery was located and the skin and subcutaneous tissues about the site were injected with approximately 0.5 c.c. of 2 per cent novocain solution. A sharp, short-beveled, 20-gauge Luer needle, connected by lead tubing to a Hamilton manometer, was inserted. Only occasionally was any marked discomfort experienced by the subject. Venous pressure was recorded through a 20-gauge needle inserted in the antecubital vein and connected with a second Hamilton manometer barrel fitted with a rubber membrane. Respiration was recorded by transmitting the pressure changes in a rubber bag, inflated with air to a pressure of 2 to 3 mm. Hg, inside of a linen binder placed loosely about the chest, to a third Hamilton manometer barrel fitted with a rubber membrane. The beginning and end of carotid sinus stimulation and of syncope and convulsions, were recorded by passing a card in front of the camera. Drugs, such as atropine sulfate and paredrine hydrobromide,* were given intravenously, and the beginning and end of the injection were recorded.

Stimulation of the carotid sinus was carried out digitally. Occasionally, in sensitive persons, the palpation necessary to locate the sinus caused mild stimulation. Pressure on the sinus was often gentle, sometimes firm, but in no case was it sufficient to shut off the arterial supply, as evidenced by the fact that pulsation could be felt above the site of pressure. Even though the artery may have been partially occluded in rare instances, the observed effects on pulse rate and arterial pressure were not attributable to partial closure of the artery, for complete closure could be carried out either above or below the site of the carotid sinus without their occurrence. Pressure below the sinus sufficient to reduce pressure within it regularly called forth a mild rise of arterial pressure and pulse rate.

*Paredrine hydrobromide for these studies was kindly supplied by Smith, Kline & French Laboratories.

CIRCULATORY RESPONSES

The response to digital pressure upon the carotid sinus was recorded in each instance before and after the intravenous injection of 2.5 mg. of atropine sulfate and, at some other time, before and after 10 mg. of

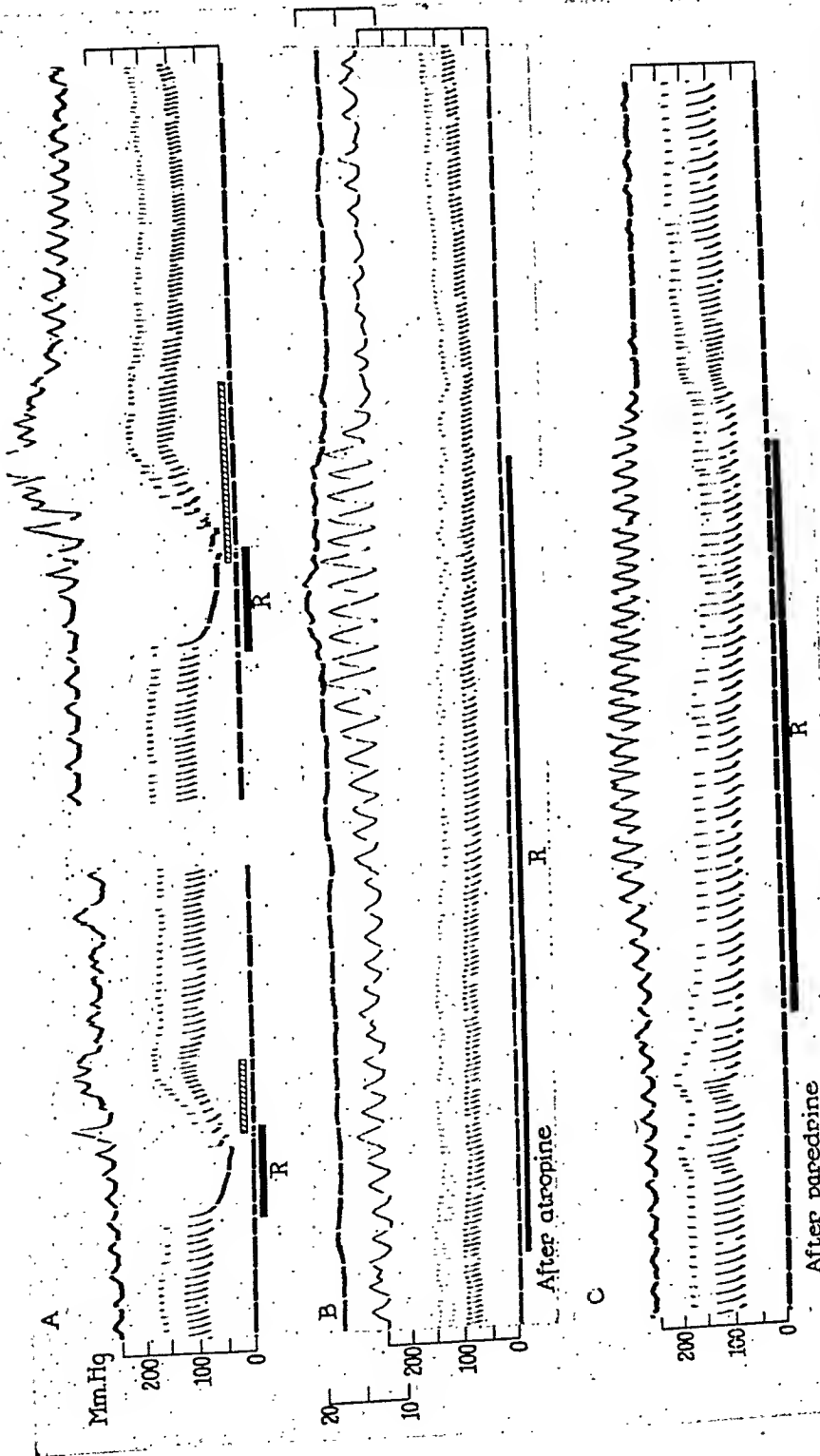


Fig. 1.—In this figure and in the subsequent ones, the upper curve represents respiration (inspiration is the upstroke), as recorded by a pneumograph, and the lower curve, arterial pressure, as recorded by a Hamilton manometer from the radial artery. The base line is interrupted at intervals of five seconds. The solid line below the base line indicates the duration of stimulation of the carotid sinus (R—right side, L—left); the dashed line above shows the duration of the pulse and convulsions. An example of the vagal response to carotid sinus pressure is shown (A). Slowing of the pulse and convulsions were prevented by atropine (B), but the depressor response was marked. Paredrine also prevented convulsions, but moderate slowing and some fall in arterial pressure persisted (C). Note hyperpnea, followed by shallow, irregular respirations (B) and apnea (C). The curve above respiration (B) is a record of venous pressure.

paredrine hydrobromide. Paredrine was employed in preference to other sympathomimetic substances because its effect is supposed to be unaccompanied by cortical stimulation.^{22, 23}

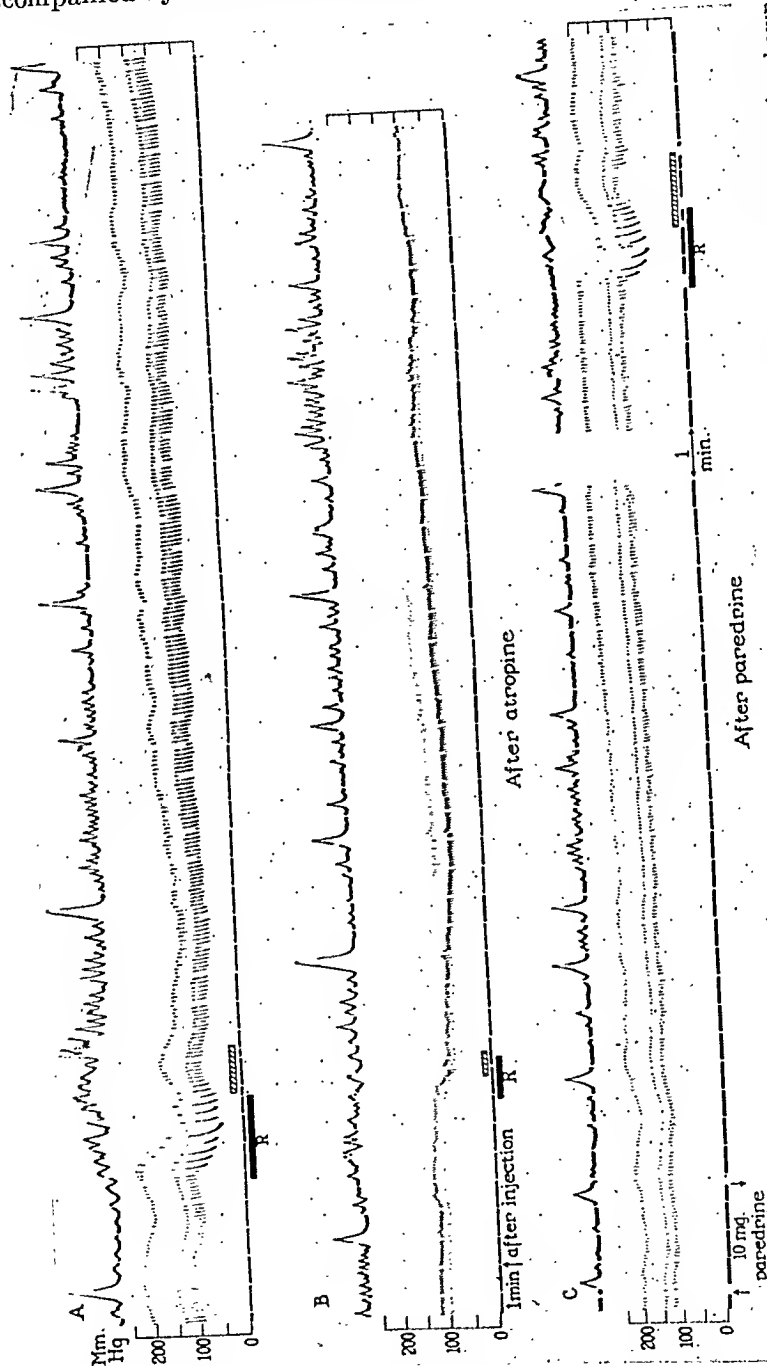


Fig. 2.—An example of the coexistence of vagal and depressor responses with syncope and convulsions is shown (A). Atropine prevented the vagal, but enhanced the depressor, response (B). Syncope and convulsions persisted. Paredrine caused a moderate rise in arterial pressure and prevented the depressor, but not the vagal, response and syncope (C).

Bradycardia, and often asystole of three to seven seconds' duration, and a fall in arterial pressure constituted the evidence for circulatory effects of carotid sinus stimulation. If both pulse rate and arterial pressure returned promptly to their previous levels, the fall in arterial

pressure was taken to be the result of slowing of the heart, and the response was called "vagal" (Cases 1, 2, 3, Fig. 1A). Additional evidence that a fall in arterial pressure was, in these instances, mainly dependent upon the bradycardia was the fact that, when atropine prevented the slowing of the heart, it also prevented, to a large extent, the fall in arterial pressure (Fig. 1B).

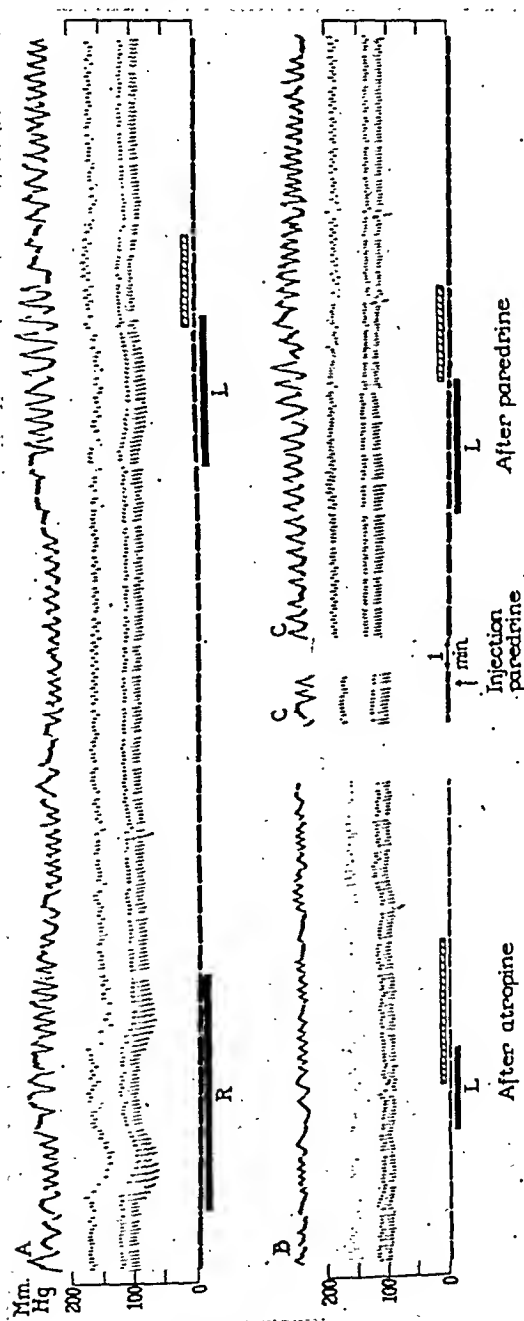


Fig. 3.—"Cerebral type" of response to stimulation of the carotid sinus is shown. Syncope and convulsions failed to occur in the presence of moderate circulatory changes on stimulation of the right side, but occurred promptly in the absence of circulatory changes on stimulation of the left (A). Atropine (B) and paredrine (C) failed to prevent syncope and convulsions.

In a considerable number of instances the fall in arterial pressure outlasted the slowing of the heart (Cases 4 to 15, Fig. 2A). A "depressor," as well as a "vagal," response was obviously present, for the intravenous injection of atropine prevented the slowing of the heart

rate but not the fall in arterial pressure. Under the influence of this drug, the fall in pressure was often greater than before its injection (Fig. 2B). In two instances (Cases 4 and 6), the arterial pressure remained low for several hours. The injection of paredrine had the opposite effect—the “depressor” reaction was abolished, but the “vagal” effect persisted even though it was usually less intense (Fig. 2C). A purely depressor response was not observed in the present study except after the administration of atropine. Its occurrence has, however, been reported.^{8, 10, 18, 24} It should be noted that the right and left carotid sinuses of a given person often exhibit very different degrees of sensitivity, and may even give rise to qualitatively different responses (Figs. 3 and 4, Table I).

Relation of Circulatory Changes to Syncope.—In the presence of marked circulatory disturbances caused by carotid sinus stimulation, it seemed likely that the occurrence of syncope was attributable to cerebral anoxemia due to asystole and a fall in arterial pressure. This belief was strengthened by the fact that when circulatory changes failed to occur or were very slight after the administration of atropine or paredrine, syncope, too, failed to develop (Fig. 1).

There were, however, five subjects (Cases 13, 14, 15, 16, and 17) who had syncope without circulatory disturbances. Three of these had marked circulatory changes, to which syncope was attributed before atropine or paredrine was given, but, when syncope persisted in spite of the prevention of marked circulatory disturbances by means of these drugs, it became clear that the two were not related. Weiss and Baker¹⁷ have described similar instances.

In two instances (Cases 16, 17), syncope with or without convulsions was frequently observed to follow digital pressure on the carotid sinus in the *absence* of significant systemic circulatory change (Figs. 3A, 4B). Syncope occasionally occurred after five, but usually after ten or fifteen, seconds of pressure. The administration of atropine and paredrine did not prevent the occurrence of syncope (Figs. 3B and C). These observations demonstrate that there is a “cerebral” type of carotid sinus syncope, for the syncope was shown not to be related to circulatory disturbances.

The type and degree of circulatory changes elicited in these patients by stimulation of the right and left carotid sinuses differed markedly. That syncope and convulsions may occur on stimulation of the side which produces the lesser degree of circulatory change and may fail to occur on stimulation of the side which causes the more marked circulatory response (Figs. 3 and 4, Table I) makes it obvious that the occurrence of syncope and convulsions with carotid sinus stimulation is not always related to an impaired flow of blood to the brain.

Venous Pressure.—Observations upon animals’ mesenteric veins which were isolated from the circulation but left in connection with their

nervous attachments have shown that contraction takes place during stimulation of the carotid sinus.^{25, 26, 27} Studies of the effect of stimula-

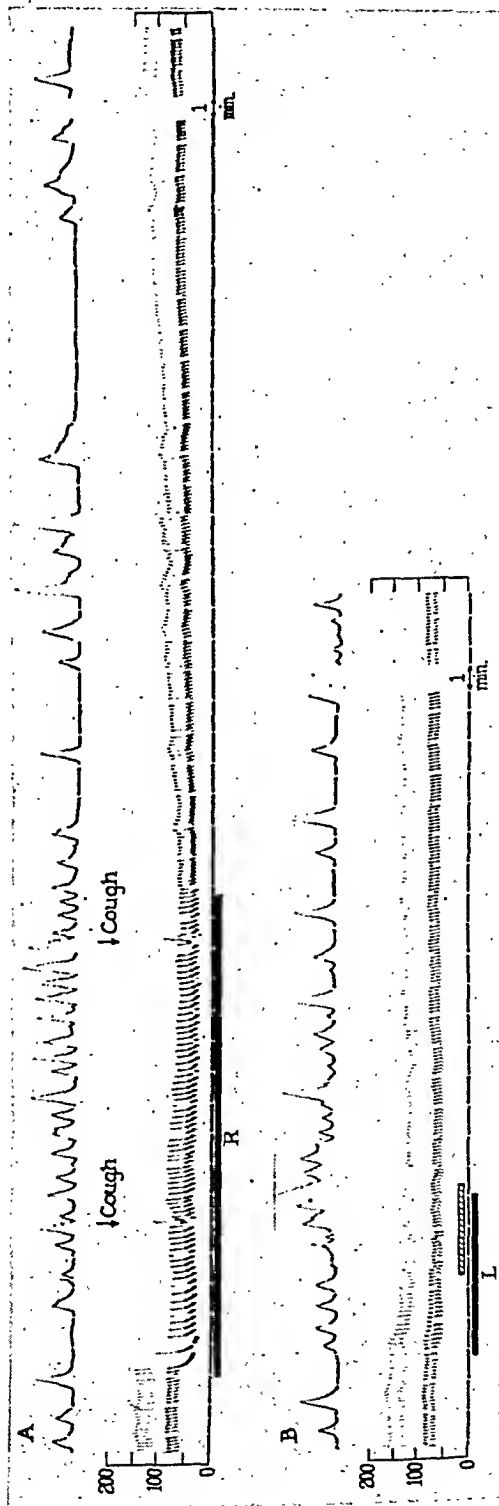


Fig. 4.—A second example of "cerebral" response is shown. Marked vagal and depressor responses followed stimulation on right side, without syncope or convulsions (A). Stimulation on the left was followed by syncope and convulsions in the absence of significant circulatory changes (B).

tion of the carotid sinus in man upon venous pressure are too few to draw conclusions. A rise during convulsions only,²⁸ a fall with slowing of the heart,²⁹ and failure to change during the cerebral type of carotid sinus

syncope¹⁸ have been reported. The changes were independent of arterial pressure.

In seven patients with a vagal and depressor type of circulatory response, the venous pressure rose promptly, but slightly (1 to 2 cm. of water), as the heart rate slowed and the arterial pressure fell, and returned quickly to the previous level along with the heart rate and arterial pressure. A rise in venous pressure always preceded syncope and convulsions, even in one instance of a purely cerebral type. During pressure on the common carotid artery *below* the carotid sinus, a slight fall occurred, together with a rise in arterial pressure and heart rate. In each case the change in pressure was in a direction that might accompany the probable changes in cardiac output.

RESPIRATORY RESPONSES

In man, hyperpnea occurs quite regularly on pressure in the region of the carotid sinus, independently of circulatory changes, and may be elicited in nearly all normal persons,^{36, 37, 38} as well as in those who have an abnormal circulatory response to carotid sinus pressure.^{18, 39} Some observers^{18, 28} have stated, however, that the incidence of hyperpnea is greater in elderly and arteriosclerotic persons. In order to clarify this point, two groups of persons were studied, one elderly, the other young.

The respiratory changes caused by digital pressure in the region of the carotid sinus in fourteen elderly patients in the present study who also exhibited marked circulatory responses were not different from those which occurred in persons who did not exhibit circulatory changes or those reported previously in man. A marked increase in the depth, with little or no increase in the rate, of respiration occurred. Apnea, as the initial response, was not observed, regardless of the type of circulatory response. Hyperpnea occurred with the cerebral (Fig. 3), as well as with other types of syncope and, in the absence of syncope, both before and after the administration of atropine and paredrine (Fig. 1). It seemed to be independent, likewise, of circulatory change.

In those instances in which syncope and convulsions were prevented by the administration of atropine or paredrine, it was possible to observe respiratory changes during prolonged stimulation of the carotid sinus. The respiratory excursions began to increase in depth within 5 to 20 seconds after pressure was applied and continued to do so until a peak was reached between 45 and 90 seconds, and then declined rapidly during the next 10 or 15 seconds. The rate of respiration usually increased two to five breaths per minute (Fig. 1). Often it remained unchanged, and, in one instance, decreased. Although pressure on the sinus was continuous, a phasic type of respiration often occurred which resembled, in some instances, Cheyne-Stokes respiration (Figs. 5A, B, C). Each succeeding hyperpneic period was, however, usually shorter and less intense than the previous one. In the intervening periods the

respiratory excursions were either shallow and irregular, with periods of apnea, or were simply shallow and slower than normal. During hyperpnea, dizziness, "lightheadedness," a burning sensation in the

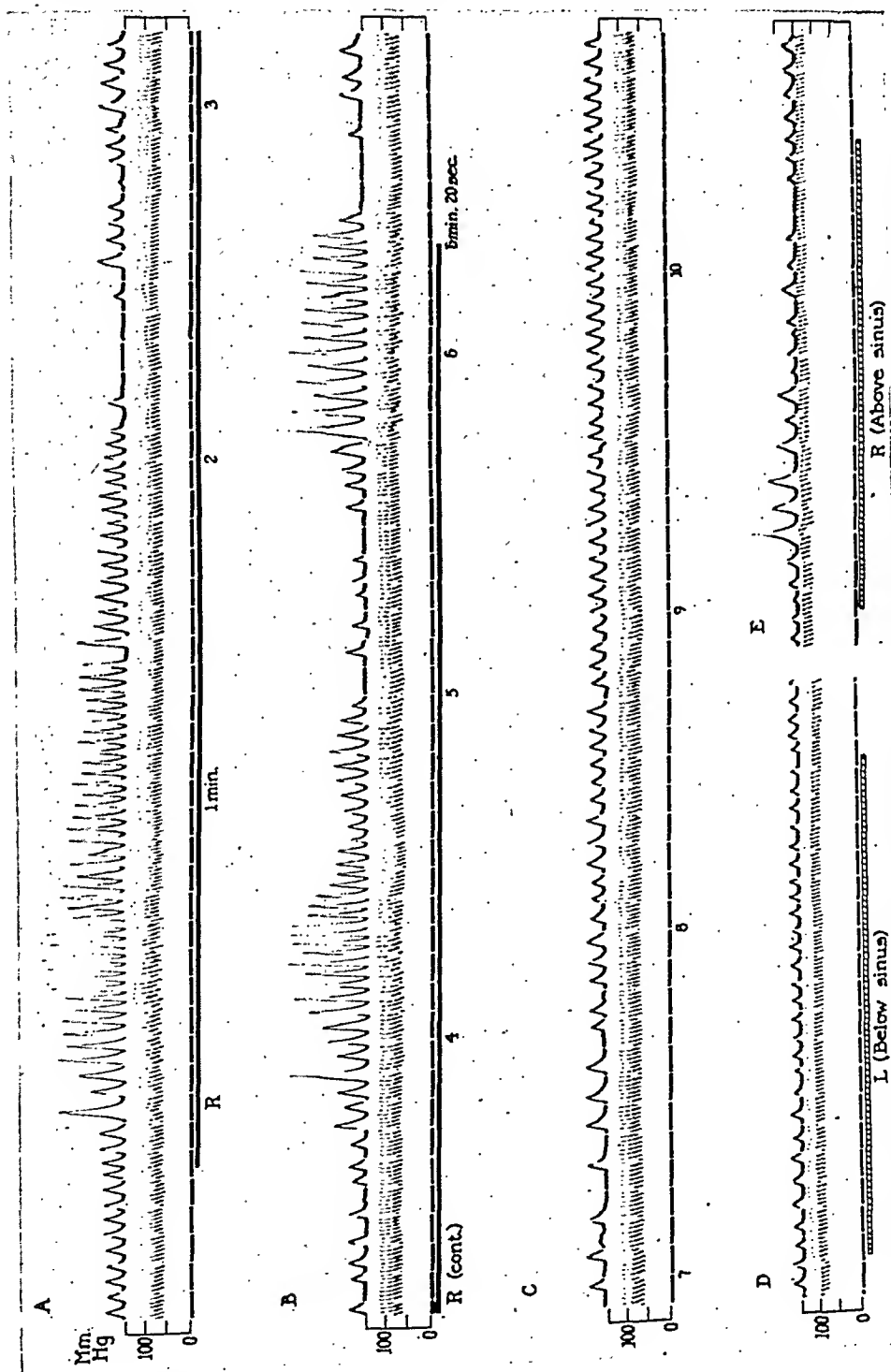


Fig. 5.—Periods of hyperpnea, followed by periods of apnea and irregular breathing induced by continuous prolonged pressure upon the carotid sinus of a young adult are shown (A, B, and C are three immediately successive portions of a continuous record). Circulatory changes occurred only at the height of hyperpnea. Respiration was not altered by digital pressure below the carotid sinus (D) and only slightly during the first few seconds of pressure above (E).

face, tingling in the extremities, and, in many instances, profuse perspiration of the hands and flushing of the face occurred. The degree of hyperpnea appeared to be sufficient to account for these symptoms.

Changes in the character of respiration were not observed when pressure was applied to the common carotid artery above or below the level of the carotid sinus (Fig. 5D, E), except for occasional deep breaths just after pressure was begun (Fig. 5E). Pain as a result of digital pressure was clearly not responsible for the stimulation of respiration, for painful stimuli (strong pressure on the trachea or the anterior border or belly of the sternocleidomastoid muscle, or deep pressure elsewhere in the neck) did not elicit a similar response. Furthermore, when the skin in the region of the carotid sinus was anesthetized with a 1.5 per cent solution of procaine, respiratory stimulation could still be elicited by pressure over the carotid sinus.

Thirty-five young persons were also studied. None of them exhibited pronounced circulatory responses to carotid sinus pressure. Twenty-two (thirteen men and nine women) were patients from the wards, and thirteen (eight men and five women) were members of the house and nursing staffs. Their ages ranged from 15 to 30 years. In all but five persons, the hyperpnea in response to carotid sinus pressure was similar in degree to that which occurred in the older patients. The respiratory change was usually not preceded by significant circulatory changes, but occasionally there were a slight rise in arterial pressure (5 to 20 mm. Hg) and a slight fall in pulse rate (6 to 20 per minute). When phasic respiration was induced by prolonged pressure on the sinus, changes in the character and rate of the pulse occurred only during the height of the hyperpneic periods, and subsided during the apneic periods (Figs. 5A and B). This phenomenon also occurs with true Cheyne-Stokes respiration.⁴⁰ Observation of these two groups tends to confirm the view expressed by Danielopolu and his co-workers, namely, that hyperpnea in response to carotid sinus pressure occurs in most normal persons, young or old, male or female.

Mechanism of Production of Hyperpnea.—There is, in the literature, general agreement that changes in the arterial pressure within the carotid sinus influence respiration as well as circulation. The circulatory changes described in man in response to pressure on the carotid sinus have quite regularly resembled those observed in animals, but respiratory reactions in man are not so easily correlated with the studies on animals. In animals under anesthesia, an increase in arterial pressure within the carotid sinus gives rise to apnea or slowing of respiration,^{12, 13, 30-35} but hyperpnea is the regular response to pressure in the region of the carotid sinus in man.

The conditions under which studies of respiratory response to stimulation of the carotid sinus and carotid bodies in animals have been carried out differ, however, from those under which man has been studied chiefly in three respects: (1) the animals were anesthetized, (2) the pressure changes were applied within the carotid sinus, rather than upon it from the outside, and (3) anatomic and physiologic

arrangements were carefully made so that stimulation of the carotid sinus would not affect the carotid body. Any of these differences may account for the fact that apnea, rather than hyperpnea, usually occurs in animals when there is an increase in pressure in the carotid sinus.

An attempt was made to investigate the first of these differences by testing the respiratory effects of pressure on the sinus while the subject was under the effect of general anesthetic agents, and to study the third by using local anesthesia to separate the activities of the carotid sinus from the carotid body. Concerning the anesthetic agents employed in animal studies, it is generally agreed that the barbiturates depress the carotid sinus, vasomotor^{14, 41} and respiratory reflexes,⁴² and that chloralalane is the one of choice,^{42, 43} but lack of agreement exists concerning the use of morphine-pernocton anesthesia.^{43, 44} In human beings, barbiturates and many of the inhalation anesthetic agents are reported to depress, and morphine to increase, the circulatory reflex.⁴⁵

The effect of barbiturate anesthesia was studied on six patients who showed respiratory, but no circulatory changes in response to carotid sinus pressure. Anesthesia of sufficient degree to prevent any response to painful stimuli was induced by injecting, intravenously, evipal (4 cases) or sodium pentothal (2 cases) (0.6 to 1.0 Gm.). A transient, slight fall of arterial pressure, without significant change in pulse rate, usually followed the injection. Hyperpnea of the same degree and after the same interval as in the unanesthetized state was elicited in every case. In the doses used, barbiturate anesthesia plainly did not affect the respiratory reaction. In one instance a preanesthetic dose of $\frac{1}{4}$ grain of morphine and $\frac{1}{100}$ grain of scopolamine was followed by drowsiness, but failed to prevent the appearance of hyperpnea after pressure on the carotid sinus. It seems unlikely, therefore, that general anesthesia is responsible for the differences observed between man and animals.

In studies on animals, great care has been taken not to alter the blood supply to the carotid body during stimulation of the carotid sinus. The method generally employed has been to exclude the carotid body from the circulation, and to perfuse it independently. Under these circumstances, respiration is depressed when there is an increase in intrasinal pressure. When the blood supply to the carotid body is, however, deliberately reduced, respiration is stimulated.^{46, 47} In man the two structures lie so close together that during pressure upon the carotid sinus region the blood supply to the carotid body may obviously be partially obstructed. It is, therefore, quite possible that the hyperpnea observed in man may arise as a result of stimulation of the carotid *body* rather than of the carotid *sinus*.

To test this possibility, the regions about the carotid sinuses of four persons were anesthetized with a 1.5 per cent solution of procaine to learn whether the respiratory response, like the circulatory response to

pressure upon the carotid sinus, could be prevented. Three exhibited marked circulatory and respiratory changes, and one had respiratory changes only. The degree of success of the block was tested by injecting 0.11 mg. per kilogram of body weight of sodium cyanide intravenously. If hyperventilation occurred after the injection of sodium cyanide, more procaine was injected, but if there was no response, the block was considered complete. It was found that when sodium cyanide failed to elicit a respiratory reaction, pressure on the carotid sinus also failed. Circulatory responses likewise were lacking. As the anesthesia wore off, the respiratory response (hyperpnea) returned more quickly than the circulatory (cardiac slowing)—a fact which suggests that the mechanisms involved in bringing about the two responses are not identical. Together with the previous studies on animals, the observation suggests that hyperpnea, as ordinarily induced by digital pressure in man, is caused by a disturbance of the circulation to the carotid body.

Marked transient tachycardia and hypertension, lasting thirty or forty minutes, which were not affected by carotid sinus pressure, occurred after complete anesthetization of both carotid sinuses; this was to be expected, in view of Heyman's studies on dogs whose carotid sinus and aortic nerves had been sectioned.¹²

COMMENT

In persons with a hypersensitive carotid sinus reflex, syncope and convulsions seem to be brought about in at least two ways. The one which is better understood and more common is probably the result of cerebral anoxemia caused by slowing of the heart, or asystole, or a fall in arterial pressure. The second mechanism occurs in the absence of systemic circulatory changes of any significance, for which reason it has been labelled the "cerebral" type. Gross cerebral circulatory changes, as measured by a thermocouple and by differences in oxygen and carbon dioxide content of arterial and venous blood, apparently do not occur in this variety.^{18, 48} Vasoconstriction in small areas of the brain of insufficient extent to be detected by these techniques may, of course, have taken place, but it seems unlikely; for, in animals, dilatation of the cerebral vessels has been demonstrated on stimulation of the carotid sinus (increase in intrasinal pressure), and constriction only on decrease of intrasinal pressure.^{49, 50} In any event, the vasomotor reactions of the blood vessels of the brain are feeble, and do not ordinarily appear to play a large part in the control of cerebral blood flow.^{50, 51, 52}

Some evidence exists for believing that syncope occurs as the result of direct nervous transmission of impulses from the site of stimulation. Weiss believed that syncope may result from reflex inhibition of a center of consciousness.⁵³ Electroencephalographic studies indicate that some alteration in cerebral activity occurs during the "cerebral" type of carotid sinus syncope, but a distinction cannot be drawn between this type of syncope and that associated with systemic circulatory change.⁵⁴

The regular occurrence of hyperpnea in man is of interest because it differs from what has been reported in studies on animals. With the exception of Danielopolu and his co-workers,^{37, 38, 39} it is generally agreed that apnea is the usual response to a rise in *intrasinus* pressure. Schmidt and Comroe³⁴ have found that if the effect of compensatory reflex areas (opposite carotid sinus and aortic bodies) is not eliminated, either by denervation or by maintaining the systemic blood pressure at a constant level, hyperpnea may occur. In the present study it seems unlikely that compensation accounts for the hyperpnea for two reasons. First, hyperpnea occurred in the absence of circulatory changes of sufficient magnitude to arouse a compensatory reaction, and, second, it occurred to the same degree and quite as promptly in two patients whose left carotid sinuses had been removed surgically⁵⁵ (Cases 12 and 14). The aortic bodies were, of course, intact in both patients.

The more likely explanation is that the crude manner in which stimulation of the carotid sinus is carried out in man, namely, by pressure on the neck in the region overlying the carotid sinus, impairs the blood flow through the carotid body. Four facts suggest that this is so. (1) The carotid body and sinus lie in close proximity in man. (2) Pressure is required for a considerably longer period of time to bring on hyperpnea than to induce cardiac slowing. (3) After local anesthetization of the region of the carotid sinus, the respiratory and circulatory responses returned independently of each other; the circulatory took longer. (4) The respiratory response (hyperpnea) corresponds to what has been found in animals when the blood flow to the carotid body is reduced. Differences between animal and human studies become, from this point of view, more understandable.

Even though the method of stimulation in man is obviously crude insofar as localization is concerned, it is surprising that standard textbooks of physiology fail to refer to the observation that hyperpnea regularly follows pressure on the neck in the region of the carotid sinus in normal persons, as well as in those with evidence of a hypersensitive carotid sinus reflex, and that it is quite independent of circulatory change.

SUMMARY AND CONCLUSIONS

1. The circulatory and respiratory responses to stimulation of the carotid sinus by digital pressure in seventeen persons with hypersensitivity of the carotid sinus were studied.

2. The common circulatory response is slowing of the heart and asystole (vagal response), together with a fall in arterial pressure (depressor response). A pure vagal response is next most common. A pure depressor response was not observed except when the patient was under the influence of atropine. Paredrine hydrobromide prevented, to a large degree, the depressor responses.

3. Two patients had convulsions without any significant circulatory change (cerebral type). In three other patients, syncope and convulsions persisted when circulatory changes were inhibited by the administration of atropine or paredrine.

4. Hyperpnea is the regular respiratory response to digital pressure in the region of the carotid sinus. Its occurrence is independent of the circulatory response. It is independent of age or sex. It is not prevented by barbiturate anesthesia, but local infiltration of the region about the carotid sinus and carotid body with procaine hydrochloride abolishes it. Prolonged stimulation is often followed by a phasic type of respiration similar to Cheyne-Stokes breathing.

5. Evidence is presented for the belief that hyperpnea after pressure on the neck in the region of the carotid sinns in man may be caused by a disturbance of the blood supply to the carotid body, rather than by mechanical stimulation of the carotid sinns.

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EFFECT OF HIGH-PROTEIN DIET AND UREA ADMINISTRATION ON THE BLOOD PRESSURE OF NORMAL DOGS AND OF DOGS WITH EXPERIMENTAL RENAL HYPERTENSION

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A NUMBER of observations have been made to ascertain the effect of high-protein diet on renal function and structure. Newburgh¹ and others produced renal lesions in animals by high-protein feeding. Relatively few investigators have studied the question of blood pressure response to high-protein diet. Almost all agree that excessive protein intake does not cause blood pressure elevation in normal, intact animals. An exception appears in the work of Nuzum, Osborne, and Sansum,² who attributed a blood pressure rise in rabbits to renal injury produced by excessive urinary acidity from a high-protein, acid ash diet (oat protein), or excessive urinary alkalinity from a high-protein, alkaline ash diet (soy bean). Anderson,³ however, failed to find any blood pressure increase in normal rabbits which were maintained on a high-protein diet for nearly a year, or in rabbits in which 60 per cent of the kidney tissue had been removed. Chanutin and Ludwig⁴ rendered rats hypertensive by subtotal nephrectomy, and, in subsequent feeding experiments, considered the type of protein component an important factor in the incidence of hypertension in these animals.

These experiments on rabbits and rats present three general disadvantages: first, the relative uncertainty of sustained hypertension after partial renal ablation; second, lack of suitable methods for repeated systolic and diastolic blood pressure observations; and, third, the fact that rabbits and rats are unaccustomed to high-protein diets.

More recently, Verney and Vogt⁵ reported rises of blood pressure after feeding meat, urea, and salt to dogs which had been rendered hypertensive by the application of silver clamps to the renal arteries. Maelaehlan and Taylor⁶ studied a single dog which was made hypertensive by the application of a cast to one kidney and removal of the other. Repeated rises of mean blood pressure followed meat and urea feeding. Philipsborn, Katz, and Rodbard⁷ found that high-protein diets had no effect on the blood pressure of normal dogs, but a single animal out of four with severe hypertension showed a sharp rise of systolic and diastolic blood pressure on a meat diet. Smaller elevations

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of blood pressure occurred in two repetitions of this original observation. A high-protein diet had no effect on the blood pressure of the other three hypertensive dogs, or on three additional dogs with mild hypertension.

It is the purpose of this paper to describe the blood pressure reactions of normal and hypertensive dogs to the administration of large amounts of meat and urea.

METHODS

The dogs were large mongrels or hounds. An effort was made to select dogs with long, slender legs. Only quiet animals were used. Each dog was kept in an individual cage and fed on a standard kennel ration.*

Hypertension was produced by the method of Goldblatt, et al.⁸ One of the renal arteries was exposed by means of a flank incision, a clamp was placed on it and tightened until no pulsations distal to it could be felt, and then the screw was released three-quarters to one and one-half turns. About two weeks later a similar procedure was done on the other side. Five months to six years elapsed between the completion of the last stage of the operation and the beginning of the experiments described in this report.

Blood pressures were taken by direct puncture of the femoral artery, and recorded with the Hamilton manometer.⁹ The animals were trained to lie quietly, and the needle was inserted into the femoral artery without anesthesia. As a rule, this procedure disturbed the animals very little, for all of them had been trained for at least five months before the beginning of the experiments.

Blood urea estimations were made in duplicate by the method of Van Slyke and Cullen.¹⁰ None of the animals had enough renal insufficiency to cause an abnormally high blood urea.

EFFECT OF FEEDING A HIGH PROTEIN DIET OVER A PROLONGED PERIOD

Four hypertensive and two normal dogs were selected. One of the hypertensive dogs was accidentally killed and another became pregnant, so that only two hypertensive and two normal dogs were left to complete this study. Blood pressures were taken once or twice a week throughout the experiment. For two weeks the dogs were kept on the regular kennel ration, and then the diet was changed to 36 Gm. of lean raw beef per kilogram of body weight for five weeks. The amount was then increased to 73 Gm. per kilogram for four weeks, and, finally, during the last two weeks, they received 110 Gm. of meat per kilogram. This amounted to more than 4 pounds of meat a day for the larger dogs. A second control period of eight weeks on the kennel ration finished the experiment. All of the dogs gained weight during the second and third meat-feeding periods. A maximum urea level of 100 mg. per 100 c.c. of blood was observed in one of the hypertensive dogs while it was on the meat diet. Fig. 1 shows all of the blood pressures and weights during this experiment. One of the hypertensive dogs (No. 42) seemed to show a constant rise in blood pressure while on the meat diet, but his pressure did not fall when he was changed back to the kennel ration. In the other animals no definite changes were noted.

*Cracklins, shredded wheat, oatmeal, buttermilk, bran, alfalfa salt, cod-liver oil, and meat scraps. Approximate composition: protein, 52 per cent, fat, 6 per cent carbohydrate, 36 per cent, fiber, 4 per cent.

TABLE I

BLOOD PRESSURES BEFORE AND AFTER A LARGE MEAL OF LEAN RAW MEAT
(Dogs 37, 40, 42, and 44 Had Goldblatt Clamps on Both Renal Arteries; Dogs 49 and 53 Were Normal)

DOG NO.	PRECEDING DAY	BEFORE MEAL	ONE HOUR AFTER MEAL	TWO HOURS AFTER MEAL	FOUR HOURS AFTER MEAL	TWENTY-FOUR HOURS AFTER MEAL
37	225/130	240/130	220/130	240/130	230/125	260/155
40		200/115	230/120	200/115	220/120	220/120
42	265/150	280/160	300/170	280/155	240/155	280/170
44		245/130	230/130	270/140	245/130	245/130
49	190/100	210/100		200/105	180/ 90	200/100
53	180/100	200/100	180/ 90		205/ 95	215/115

FIG. 2 INTRAVENOUS UREA & B. P.

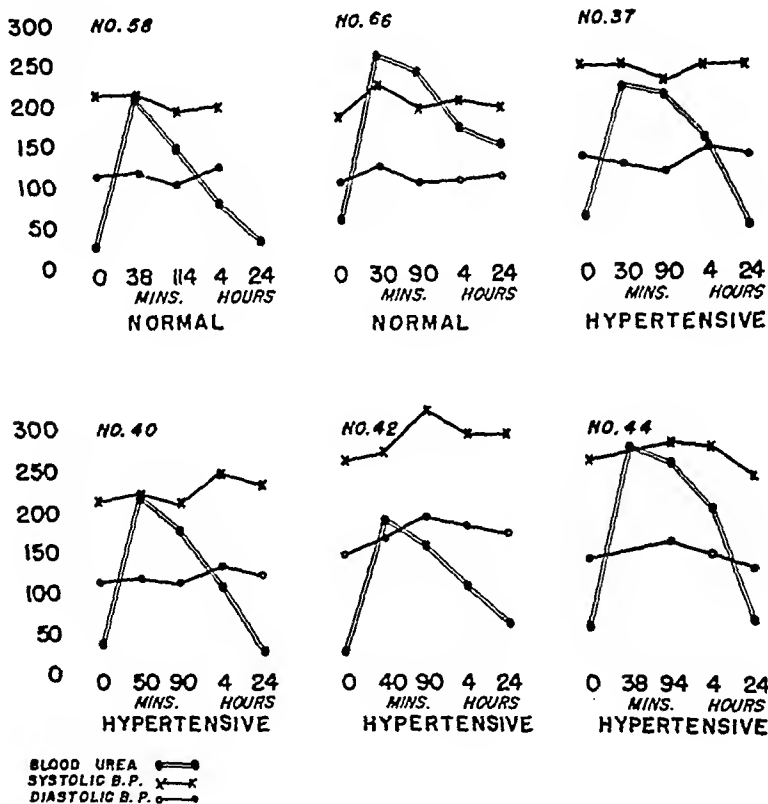


Fig. 2.—Graphic record of blood pressure and blood urea after intravenous administration of urea to normal and hypertensive dogs.

cent solution. The urea was given by means of a small rubber tube which was inserted intravenously before the beginning of the experiment, so that no discomfort to the animal accompanied the injection. The blood pressure and blood urea were ascertained at about one-half hour, one and one-half hours, four hours, and twenty-four hours after the urea injection. There was always a marked rise in blood urea, but the level promptly returned to normal within twenty-four hours. The

blood pressure and blood urea changes are shown in Fig. 2. One of the normal dogs showed a slight rise in blood pressure, and the other showed no definite change. One of the hypertensive dogs (No. 42) showed a definite rise in blood pressure, another (No. 44) showed a slight rise, and two showed no change.

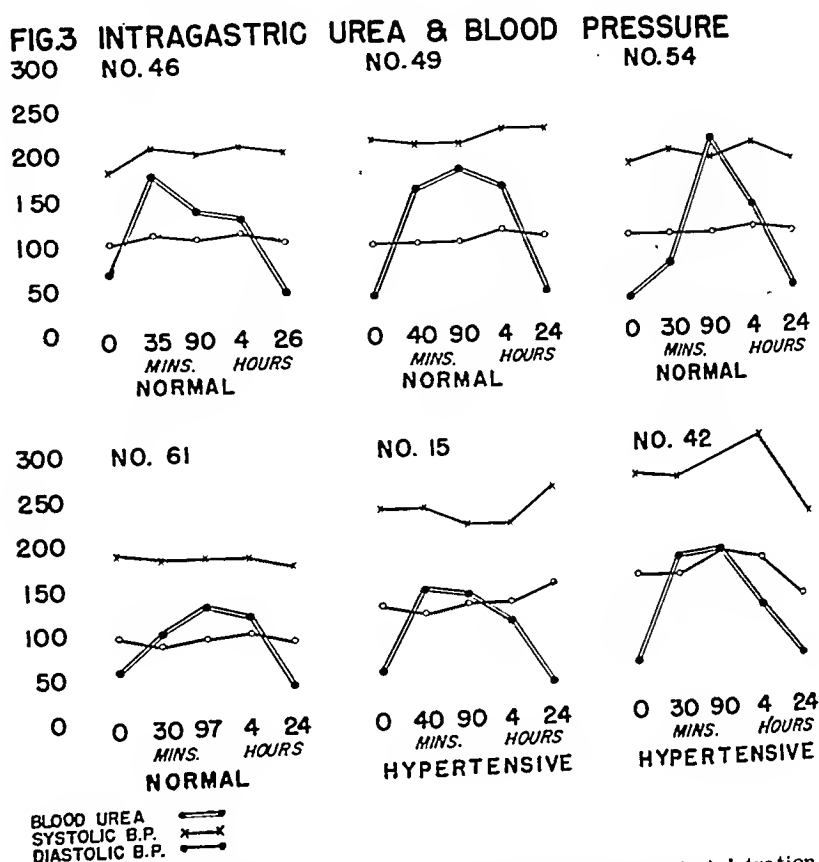


Fig. 3.—Graphic record of blood pressure and blood urea after administration of urea by stomach tube to normal and hypertensive dogs.

EFFECT ON BLOOD PRESSURE OF UREA ADMINISTERED BY STOMACH TUBE

Two hypertensive and four normal dogs were used for this experiment. The basal blood pressure and blood urea levels were ascertained, and each dog was given $1\frac{1}{2}$ Gm. of urea per kilogram of body weight by means of a stomach tube. Subsequently, blood pressure and blood urea observations were made at approximately one-half hour, one and one-half hours, four hours, and twenty-four hours. In each case there was a prompt and marked rise in blood urea, but the level returned to normal within twenty-four hours. The blood pressure and blood urea changes are shown in Fig. 3. In only one of the dogs (No. 42), a hypertensive animal, was there a definite change in blood pressure. In this dog the systolic pressure rose approximately 50 mm. Hg and the diastolic pressure approximately 25 mm. Hg one and one-half hours after urea administration.

DISCUSSION

In these experiments, prolonged meat feeding, the feeding of a single, large, meat meal, and the administration of urea by vein or by stomach tube failed to produce consistently significant blood pressure changes in normal and hypertensive dogs. One of the hypertensive dogs (No. 42) showed a moderate elevation of blood pressure during each of the experiments. However, the blood pressure failed to return toward the normal level during the eight-week control period after the prolonged meat diet. In the other hypertensive and normal dogs the changes were either insignificant or inconstant. These results are similar and comparable to those of Philipsborn, Katz, and Rodbard,⁷ who observed a significant elevation of blood pressure in only one of their hypertensive dogs. Our results differ somewhat from those of Verney and Vogt,⁵ who fed hypertensive dogs meat, salt, and urea, and produced slight changes in the systolic blood pressure. Their dogs were rendered hypertensive by the method of Goldblatt, et al.,⁸ and the blood pressures were taken by the Van Leersum loop method.¹¹ In two dogs with bilateral renal ischemia the blood pressure rise was 24 mm. Hg and, in two of three dogs with a single ischemic kidney, 16 and 20 mm. Hg, respectively. The third dog of this last group failed to show any blood pressure change. In our experience, systolic blood pressure changes of this order occur spontaneously in both normal and hypertensive dogs.

The observation of Maelachlan and Taylor⁶ on a single dog which had been rendered hypertensive by a cast on one remaining kidney requires brief comment. These investigators failed to state what blood pressure method was used, but, assuming that they measured the mean arterial pressure by arterial puncture, the rise may be considered significant, particularly when the same order of response occurred twice, with a return to original levels each time. It would be interesting to know whether or not this experiment could be repeated on other dogs. The occasional hypertensive response to meat feeding in dogs which have been rendered hypertensive by the Goldblatt method may be caused by poor development of the capsular circulation after operation, and, conversely, failure of response in the Goldblatt type of animal may be associated with an excellent capsular collateral circulation. Other indirect evidence suggests the same thing. A previous study by Jolliffe and Smith,¹² later confirmed by Van Slyke, Rhoads, Hiller, and Alving,¹³ showed that dogs have a higher urea clearance on a high-protein diet than on a low-protein diet. The latter group of investigators added the observation that the urea clearance was found to vary in direct proportion to renal blood flow. It seems not unlikely that some dogs with renal artery clamps will develop a less adequate capsular collateral circulation than others, and hence relatively inadequate renal blood flow after a large protein meal. In such a case, added degrees of hypertension may follow meat feedings. This suggests the advisability of further meat-feeding experiments on dogs which have been rendered hyperten-

sive by placing a cast on one kidney and removing the other. In such an experiment, perirenal collateral circulation would not occur.

It seems clear from the literature and our own observations that meat feeding will not bring about a blood pressure rise in normal dogs. The status of this question in respect to dogs with experimental hypertension produced by reduced renal blood flow is not clear, but it may possibly be related to the degree of re-established capsular circulation.

SUMMARY

The administration of a high-protein diet (lean raw meat) to normal and hypertensive dogs for a long or short period of time failed to produce a consistent rise or fall in systolic or diastolic blood pressure.

The administration of urea, intravenously or by stomach tube, to normal and hypertensive dogs likewise failed to produce any significant change in blood pressure.

In one hypertensive dog there was a slight to moderate rise of systolic and diastolic blood pressure after each of the four experimental procedures.

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CARDIAC COMPLICATIONS IN ACUTE GLOMERULONEPHRITIS

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INVOLVEMENT of the heart in acute glomerulonephritis has been recognized for many years, but until recently very little attention has been given to it. In 1879, Goodhart¹ reported five cases of "scarlatinal dropsy." Necropsy was done in four of these cases and dilatation of the right and left sides of the heart was found. In one case severe anasarca was present. Goodhart was unable to find any evidence of valvular heart disease in these cases and concluded that the cardiac failure was caused by "sudden peripheral obstruction in the circulation and degenerative changes in the cardiac muscle."

In 1881, Silbermann² reported five cases of acute nephritis in which there were hypertrophy and dilatation of the left ventricle. In one of these cases there was pulmonary edema. Steffen,³ in 1882, reported a case of acute nephritis in which severe dyspnea and cyanosis were observed. In 1889, Hutinel⁴ stressed the importance of considering the possibility of acute nephritis in every case of acute cardiac dilatation in which there is no other demonstrable evidence of cardiac disease. Nobécourt and Voisin,⁵ working in Hutinel's Clinic in 1909, collected data on twelve cases of acute nephritis in which dilatation of the heart was noted. They agreed with Hutinel that when no valvular lesion can be found, cardiac failure should be considered pathognomonic of acute nephritis. Nobécourt and Voisin expressed the belief that the hypertrophy and dilatation of the left ventricle in these cases could not be ascribed to hypertension alone, but that the generalized infection was an important factor.

In 1917, Franke⁶ reported sixty-seven cases of acute nephritis in which roentgenographic examination of the heart had been made. In 75 per cent of these cases there was cardiac enlargement which was believed to be a combination of hypertrophy and dilatation. Volhard⁷ observed evidence of myocardial insufficiency in the first few days of acute nephritis. Clinically, he reported strong heart action, accentuation of the second sound at the base, presystolic gallop rhythm, and, fairly frequently, a systolic murmur at the apex caused by relative myocardial insufficiency and stretching of the mitral ring. The apical impulse was heaving, and the area of cardiac dullness was increased. Volhard men-

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tioned the grave prognostic significance of a sudden fall of blood pressure or a considerable acceleration of the pulse rate in acute nephritis. At necropsy he observed dilatation of the left ventricle in these cases.

In 1920, Alwens and Moog⁸ studied four cases of acute nephritis by means of serial orthodiagrams, and demonstrated cardiac enlargement during the acute infection, with return to normal size when the patients recovered. They expressed the belief that the enlargement was caused by acute dilatation and by hydropericardium.

Christian and O'Hare,⁹ in 1925, concluded that any cardiac enlargement, murmurs, or arrhythmia observed in a patient who had acute nephritis was coincidental, and in no way related to the nephritis. They maintained that, except in rare cases, the heart and circulation are unchanged in acute nephritis.

In 1930, Levy¹⁰ reported ten cases of acute nephritis in which there was cardiac involvement. He concluded that, in the absence of disease of the valves or coronary arteries or any other demonstrable cardiac pathologic change, the sudden appearance of cardiac decompensation, with dilatation of the right side of the heart, pulmonary congestion, and an enlarged liver, should make one suspect that acute nephritis is present. Levy was of the opinion that edema in some of these cases of nephritis may be attributed, at least in part, to circulatory failure.

Since then, there have been a number of interesting studies of the heart in acute glomerulonephritis. Guthrie¹¹ observed that the left ventricle was hypertrophied in a third of thirty-four cases of acute nephritis. Master, Jaffe, and Dack^{12, 13} studied thirty cases of acute glomerulonephritis with particular reference to the electrocardiographic changes. They were able to show a direct correlation between the electrocardiographic changes and the clinical and laboratory evidence of cardiovascular involvement. They concluded that in acute nephritis there is involvement of the heart, probably as a part of a general vascular disturbance. In their cases the electrocardiographic changes frequently lasted longer than the symptoms. They noted changes in the T waves similar to those which occur in occlusion of the anterior descending branch of the left coronary artery.

Langendorf and Pick¹⁴ made serial electrocardiographic studies in twelve cases of acute glomerulonephritis. Among other changes, they noted flattening or inversion of T₁ and inversion of T₄. They distinguished these abnormalities from those caused by infarction of the anterior wall of the left ventricle by the absence of changes in the S-T segment and Q wave, so frequently found in acute infarction of the myocardium. The absence of an elevation of the S-T segment in the early tracings in acute nephritis helped to obviate the confusion with alterations produced by acute pericarditis.

In 71 per cent of the cases of acute nephritis reported by Whitehall, Longcope, and Williams¹⁵ there was cardiac failure which was in many

instances out of proportion to the severity of the nephritis. In a subsequent study, Williams¹⁶ was unable to establish any correlation between the electrocardiographic changes and the signs of cardiac or renal insufficiency.

By means of electrocardiographic and teleroentgenographic studies, Hayman and Martin¹⁷ were able to find evidences of myocardial damage in half of their cases of acute nephritis.

Feller and Hnrevitz¹⁸ reported two cases of acute nephritis accompanied by cardiac failure which was predominantly left ventricular. They found that cardiac decompensation may occur early in the disease, even before clinical evidence of renal damage. They were of the opinion that many of these patients have panarteriolitis, with involvement of the vessels of the myocardium.

Rubin and Rapoport¹⁹ observed that the most frequent complication in acute hemorrhagic nephritis is cardiac, and that many patients who die in the acute attack die of cardiac failure. Of their series of fifty-five cases, severe myocardial damage was encountered in fourteen, in twelve of which there was definite cardiac decompensation. The clinical evidences of cardiac involvement and failure in these cases were dyspnea, cardiac enlargement found by physical examination and in teleroentgenograms, muffled heart tones, tachycardia, mitral systolic murmurs, gallop rhythm, enlarged and tender liver, venous engorgement, pulmonary and peripheral edema, and electrocardiographic changes indicating some degree of myocardial damage. They expressed the belief that the two factors in the acute phase of nephritis which may affect the heart adversely are myocardial damage and hypertension. Although Rubin and Rapoport observed that cardiac damage was a definite danger to life in the acute phase of glomerulonephritis, in their opinion the ultimate cardiac prognosis is good.

REPORT OF CASES

We have reviewed data on one hundred thirty-six cases of acute glomerulonephritis at the Mayo Clinic with particular reference to the cardiac complications. In twenty-two cases (16 per cent) there were obvious cardiac manifestations of varying severity. In no case was there evidence of any other etiological factor, such as rheumatic, syphilitic, or coronary heart disease, previous hypertension, or hyperthyroidism. In addition, in twelve cases (9 per cent) some cardiac involvement, probably related to the acute glomerulonephritis, was observed at necropsy, but these cases were not included because some other factor, such as coronary sclerosis, low-grade hypertension, or hyperthyroidism, was present. Fortunately, the mortality rate of acute glomerulonephritis is low, and, consequently, most of the cardiac manifestations will be those observed on clinical rather than post-mortem examination. The incidence of cardiac complications in the present

series of cases of acute glomerulonephritis is undoubtedly too low because not all of the patients were under observation from the onset of their illness. Several patients reported symptoms or signs of cardiac involvement that had occurred earlier in the course of their disease, but, since all evidences of cardiac involvement had disappeared prior to examination at the clinic, these cases were not included in the present series. If serial electrocardiograms had been taken routinely in every case of acute glomerulonephritis, the percentage of cases in which there was evidence of involvement of the heart undoubtedly would have been increased.

The following brief summaries of nine cases illustrate various cardiac complications in acute glomerulonephritis.

CASE 1.—A boy, 15 years of age, was admitted to the clinic March 9, 1939, acutely ill and stuporous. Infection of the upper part of the respiratory tract had begun February 25. On March 5, a severe headache had developed and the patient had noticed dark brown urine. On March 7, he had had chills and fever and had become mentally confused. The heart was normal to physical examination except for tachycardia and a soft, systolic murmur at the apex. The blood pressure was 160/65. Routine urinalysis showed gross blood, many granular casts, and albuminuria grade 4 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition). The concentration of urea was 92 mg. per 100 c.c. of blood. A culture of the spinal fluid was positive for Type XII pneumococcus. The clinical diagnosis was pneumococcal meningitis, with acute glomerulonephritis, hypertension, and uremia. After sulfapyridine therapy the patient improved temporarily, and the culture of his spinal fluid became negative. However, on March 15, 1939, a relapse occurred, and he died March 29. At necropsy the heart weighed 205 grams, and there was pronounced dilatation of the left auricle and ventricle. The surface of both kidneys was covered with numerous red dots. Histologic examination of the kidneys revealed such extreme swelling of the endothelial cells of the glomeruli that the capillaries of the glomerular tufts were practically obliterated. Some of the tubules contained blood and necrotic cellular debris.

CASE 2.—The patient was a woman, 30 years of age. On Dec. 6, 1930, a "cold" and a discharge from the left ear developed. On December 24, she suddenly had an attack of dyspnea, followed by a similar attack the next day. Morphine and epinephrine did not give any relief. On December 27, she had a very severe attack of dyspnea, and died of severe pulmonary congestion several hours after hospitalization elsewhere. At necropsy the pericardial cavity was found to contain 150 c.c. of clear fluid. The heart weighed 250 grams. The left ventricle was greatly dilated, but there were no other gross cardiac abnormalities. The right pleural cavity contained 1,000 c.c. of fluid, and the left pleural cavity contained 1,500 c.c. The liver extended 8 cm. below the costal margin in the midclavicular line and was moderately congested. The kidneys were congested, and histologic examination revealed large, very cellular glomeruli containing many polymorphonuclear cells within their capillaries, but very few erythrocytes. The proximal convoluted tubules showed degeneration, with some very pale nuclei and granular cytoplasm. There was severe congestion of the small blood vessels in the medulla.

CASE 3.—A man, 21 years of age, was admitted to the clinic Aug. 18, 1939, suffering from severe peripheral edema. He had been well until August 8, when he began to notice shortness of breath on exertion. On August 13 a nonproductive cough and

nocturnal dyspnea had developed, but he was able to continue working. Three days later he was unable to wear his shoes because of peripheral edema.

On physical examination, the patient weighed 275 pounds (124.7 kg.). The pharynx was injected and the tonsils were grossly infected. Severe dyspnea was noted and there was moderate edema of the ankles. Râles were heard at the bases of both lungs, and the heart was greatly enlarged to the left to percussion. There were no murmurs. The blood pressure was 160/98. Urinalysis showed albuminuria, grade 2 (on the basis of 1 to 4), gross blood, and granular casts. The concentration of hemoglobin was 10.8 Gm. per 100 c.c. of blood (71 per cent); the erythrocytes numbered 3,770,000, and the leucocytes, 6,000, in each cubic millimeter of blood. The concentration of urea was 62 mg. per 100 c.c. of blood. Roentgenographic examination of the chest revealed pronounced cardiac enlargement. The electrocardiogram showed a rate of 103, and slurred QRS, diphasic P waves, and inverted T waves in Lead III.

The diagnosis was acute glomerulonephritis with cardiac decompensation. The patient responded satisfactorily to treatment and was dismissed from the hospital Sept. 7, 1939. He was seen again on Oct. 24, 1939, at which time the results of routine urinalysis were normal except for an occasional erythrocyte. His blood pressure was 124/84, and his pulse rate, 68; clinical examination of the heart did not reveal any evidence of organic disease.

CASE 4.—A girl, 3 years of age, was admitted to the clinic Aug. 7, 1939, with albuminuria, grade 2, hyaline and granular casts in the urine, and gross hematuria. Four weeks prior to admission she had had a head cold and a temperature of 100° to 104° F. for five days. Two weeks prior to admission she had impetigo, followed by a skin eruption on the trunk and face, with a temperature of 103° to 104° F. One week prior to admission gross hematuria was noted.

Physical examination revealed enlargement of the heart to the left and a loud systolic murmur over the precordium which was transmitted to the axilla. The blood pressure was 100/40. The patient returned to the clinic in November, 1939, at which time the results of urinalysis were negative. The heart had decreased noticeably in size on physical examination, and the systolic murmur had decreased in intensity and was inconstant.

CASE 5.—A boy, 4 years of age, was admitted to the clinic March 23, 1940. He had a loud systolic murmur over the entire precordium. One month prior to admission he had had an infection of the upper part of the respiratory tract. Three weeks prior to admission gross hematuria was noted. The hematuria lasted three days and disappeared. One week prior to admission the infection of the upper part of the respiratory tract recurred. Coincident with this, a loud systolic murmur appeared and became audible over the entire precordium. Gross hematuria again was noted.

Physical examination revealed a pulse rate of 120. Albuminuria was graded 2, and the urine contained hyaline and granular casts and gross blood. The concentration of urea was 40 mg. per 100 c.c. of blood. Five days after admission the results of routine urinalysis were negative. The cardiac murmur completely disappeared and the cardiac rate decreased to 90 beats per minute.

CASE 6.—A man, 55 years of age, registered at the clinic Jan. 25, 1939. Two weeks prior to admission he had had influenza, and his temperature had been 103° F. Eleven days prior to admission otitis media developed on the left side. The eardrum ruptured spontaneously and the ear drained freely. Twenty-four hours prior to admission he had a chill, a temperature of 103° F., sore throat, and gross hematuria.

Physical examination revealed a loud systolic murmur diffusely over the precordium, but most intense at the aortic area. Albuminuria was graded 3, and gross blood was found in the urine. The concentration of urea was 26 mg. per 100 c.c. of blood. The patient was seen again in November, 1939, when clinical examination of his heart gave entirely negative results except for a slight accentuation of the aortic second sound.

CASE 7.—A boy, 11 years of age, was admitted to the clinic April 21, 1939, in a stuporous condition. He had been well until March 25 when he developed an acute sore throat which lasted three days. Enlarged, tender, cervical lymph nodes persisted. On April 12 gross hematuria was noted. Twenty-four hours prior to admission a severe headache developed and the patient became comatose. Physical examination revealed that the cardiac apex was 1.5 cm. to the left of the mid-clavicular line. The blood pressure was 160/110. Urinalysis revealed albuminuria, grade 4, granular casts, and gross blood. The concentration of urea was 52 mg. per 100 c.c. of blood. Roentgenographic examination of the thorax revealed slight cardiac enlargement and congestion of both hilar regions. When the patient was dismissed two weeks later, all signs of pulmonary congestion had disappeared, and the heart was found to be definitely smaller than at the previous examination.

CASE 8.—A boy, 17 years of age, was admitted to the clinic Jan. 22, 1939. He had been well until Dec. 20, 1938, when tonsillitis and a peritonsillar abscess developed. On Jan. 7, 1939, the abscess opened spontaneously and he felt much better. On January 10 swelling of the face and headaches appeared. Twenty-four hours prior to admission severe headaches and generalized convulsions occurred.

Physical examination revealed a loud systolic murmur at the apex. The pulmonary second sound was much louder than the aortic second sound. Râles were heard at the bases of both lungs. The blood pressure was 130/90. The urinalysis revealed albuminuria, grade 4, hyaline and granular casts, and gross blood. The concentration of urea was 26 mg. per 100 c.c. of blood. Five days after admission all signs of pulmonary congestion had disappeared completely.

CASE 9.—A girl, 10 years of age, was admitted to the clinic Jan. 13, 1939. Four weeks prior to admission she had had measles. Three weeks prior to admission a discharge from both ears developed. Physical examination revealed an extrasystole every fourth beat. Râles were heard at the bases of both lungs. Urinalysis revealed albuminuria, grade 3, granular casts, and gross blood. The concentration of urea was 94 mg. per 100 c.c. of blood. Roentgenographic examination of the thorax revealed congestion at the right hilum and right cardiophrenic angle. All signs referable to involvement of the heart disappeared completely within two weeks after admission.

COMMENT

The primary cause of death in the first case was pneumococcal meningitis, but severe dilatation of the heart may have been an important contributory factor. The only explanation for the death of the second patient was cardiac dilatation and anasarca. This case also illustrates how acute and fulminating the cardiac complication may be. In the third case, the symptoms that brought the patient to the clinic were those of cardiac decompensation, and so predominant were the cardiac symptoms that it was not until routine urinalysis was done that acute glomerulonephritis was even suspected. The possibility that renal congestion might have been secondary to cardiac congestion in this case

was considered unlikely because of the absence of any cardiac lesion before or after the patient's examination at the clinic. The hypertension was transient and coincided with the onset of the acute illness. There was no antecedent history of rheumatic fever or valvular heart disease. This case also emphasizes the importance of considering acute glomerulonephritis in every case of myocardial failure in which there is no other demonstrable evidence of cardiac disease. In contrast to the second case, the third case illustrates how rapidly the severe congestive failure may improve, leaving no residual sign of heart disease.

Cases 4, 5, and 6 illustrate minor cardiac complications, such as murmurs and slight dilatation, that disappear completely when the acute illness subsides. There were no signs of congestive failure in these three cases. In Cases 7, 8, and 9 there were also dilatation of the heart and murmurs that disappeared subsequently, but, in addition, the condition was complicated by mild pulmonary congestion.

In this series of cases no direct correlation between the severity of the nephritis and the incidence or severity of the cardiac involvement could be found. Although in most cases there was some elevation of the systemic blood pressure, there was no significant relation between such transient hypertension and involvement of the heart.

SUMMARY

Cardiac complications are fairly frequent in cases of acute glomerulonephritis, and patients who die during the acute phase may die from heart failure. Evidence of obvious cardiac involvement was observed in 16 per cent of 136 cases. The cardiac complications varied from murmurs, with or without dilatation, to manifestations of pulmonary congestion or severe cardiac decompensation. In cases in which congestive heart failure is a complicating factor, the patient may die suddenly or may improve rapidly, leaving no demonstrable evidence of organic heart disease. The hearts of patients who die from cardiac decompensation often show great dilatation, with or without hypertrophy, but dilatation usually dominates the picture. Signs of cardiac involvement may appear and disappear rapidly, and there is no apparent correlation between the severity of the nephritis, the height of the blood pressure, and the incidence or severity of the cardiac complications.

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THE PRESSOR ACTION OF PAREDRIINE; FURTHER OBSERVATIONS

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SEVERAL studies have been made of the pressor action of paredrine (p-hydroxy- α -methyl-phenylethylamine hydrobromide) on normal human subjects.¹⁻⁵ The therapeutic effect of this compound on vasomotor collapse of various kinds has also been investigated.^{3, 6, 7} In certain types of lowered blood pressure, such as that during spinal anesthesia, the administration of 5 to 10 mg. of paredrine parenterally usually produces an adequate and prolonged blood pressure increase.⁷ However, in the shocklike state which may occur with severe infections, paredrine and the closely related compound, paredrinol (N-methyl paredrine), frequently fail to produce the anticipated pressor response.^{3, 8} The effect of paredrine on the cardiovascular systems of patients with infection, but no shock, has not been previously reported. In the present study, paredrine was administered to hospital patients with various infections, but with none of the manifestations of vasomotor collapse. Cardiac irregularities were noted in some subjects after the injection of paredrine; since only one brief comment on the production of arrhythmia by paredrine¹ was found in the literature, electrocardiograms were made during many of the experiments.

METHODS

Paredrine* was administered twenty-one times to twenty patients who were on the wards of the Cincinnati General Hospital because of various infections; none showed any evidence of shock at the time the study was made. One of these patients, however, subsequently developed vasomotor collapse, and was given paredrine.

Five additional patients were studied before and during fever produced by malarial inoculation or the injection of typhoid vaccine. To ascertain the constancy of response to paredrine in a given patient, the same dose was repeated in six patients whose clinical status remained unchanged; the intervals between injections ranged from one hour to seven days. Five of these subjects were free of acute infection, and were considered normal controls. None of the twenty-eight subjects showed any evidence of cardiovascular disease.

Three-lead electrocardiograms were made with an amplifier type of electrocardiograph on thirteen of the patients before, and at intervals after, the administration of paredrine.

All procedures were carried out at the bedside, with the patient recumbent. Blood pressure was measured at one- to two-minute intervals by the auscultatory

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TABLE I
RESPONSE TO PAREDRINE OF PATIENTS WHO RECEIVED REPEATED INJECTIONS

NO.	DATE	SEX	AGE (YR.)	WEIGHT (LB.)	DOSE (MG.)	TEMP. (DE- GREES F.)	DIAGNOSIS	INITIAL B.P. (MM. HG)	B.P. INCREASE (MM. HG)	DURA- TION OF INCREASE (MIN.)	PEAK B.P. (MM. HG)
1	3/ 2/42 3/ 2/42	F	16	72	6 6	99 99	Tuberculous peritonitis	94/66 92/66	31/20 38/34	41 52	125/ 86 130/100
2	5/25/42 5/31/42	M	46	150	10 10	98.6 98.6	General paresis	120/90 118/82	96/28 122/48	32 43	216/118 240/130
3	5/31/42 5/31/42	M	37	130	8 8	97.6 97.6	Syphilitic meningitis	94/60 94/60	58/34 56/34	25 43	152/ 94 150/ 94
4	6/14/42 6/21/42	M	29	140	10 10	98.6 98.6	Syphilis of central nervous system	126/84 120/78	64/21 70/32	30 32	190/105 190/110
5	6/15/42 6/15/42	M	37	125	8 8	98.6 98.6	Convalescent	116/68 112/64	49/17 48/16	35 46	165/ 85 160/ 80
6	6/21/42 6/21/42	M	29	145	10 10	- 98.6	Convalescent	114/68 106/64	82/32 84/46	60+ 65+	196/100 190/110

method; a standard 13 cm. arm cuff was used. Paredrine was given intravenously in a dose of approximately 1 mg. per 7 kg. after the pulse rate and blood pressure reached a constant, low level. The intravenous administration of paredrine to normal subjects in approximately the dosage used in the present study has been previously reported to produce a rise in systolic blood pressure varying from 28 to 98 mm.; diastolic blood pressure increases varying from 10 to 56 mm. were noted, and the blood pressure was found to return to the initial level in from 20 to 70 minutes.^{2, 4}

In the construction of the tables, the maximal systolic and diastolic pressures which were attained were used in computing the response, although in many experiments the two pressures did not reach peak levels simultaneously. The results obtained in several of the experiments have been included in more than one table.

OBSERVATIONS

The intravenous injection of paredrine usually produced no symptoms. A few patients noted palpitation, usually in association with a clinically discernible arrhythmia. Many of the patients observed forceful heart action, and several noted rather disagreeable throbbing in the temporal region. Several patients complained of dyspnea of three to four minutes' duration, although there was no consistent change in the depth or rate of respiration. The highest blood pressure level occurred one to four minutes after injection of the drug, and the cardiac rate was definitely decreased in all but one of the patients who showed a good pressor response.

Repeated Injections.—The blood pressure response to the intravenous injection of a given dose of paredrine was fairly constant (Table I). The maximum difference in systolic pressures was noted in Case 2; the increase was 96 mm. of mercury after the first injection of 10 mg., as compared with 122 mm. after the second injection of the same amount. The diastolic pressure increase was more variable than the systolic increase, perhaps because difficulty was frequently experienced in ascertaining the exact point of change of the arterial sounds. The duration of the pressor response in the same patient was somewhat variable.

In the five subjects (Cases 2 to 6) who were used as controls, the greatest increase in systolic pressure was 122 mm., and the least increase, 48 mm. The increase in diastolic pressure varied from 16 to 48 mm. The increase in blood pressure persisted from 25 to 65 minutes.

Infections.—The nine patients with miscellaneous infections and no signs of shock showed increases in systolic and diastolic blood pressure and a duration of change which did not differ significantly from the normal range (Table II). The systolic pressure increase varied from 34 to 74 mm., the diastolic increase, from 9 to 38 mm., and the duration of the rise, from 24 to 45 minutes. Patients 7, 8, and 10 were receiving drugs of the sulfonamide group at the time the tests were made. Eleven of the patients had tuberculous infections; they received somewhat higher doses of paredrine per kilogram of body weight than the other patients (Table III). In five of the tuberculous patients, the duration of blood pressure change was twenty minutes or less (Cases

TABLE II
RESPONSE TO PAREDRINE OF PATIENTS WITH INFECTIONS
(NONTUBERCULOUS INFECTIONS)

CASE	DATE	SEX	AGE (YR.)	WEIGHT (LB.)	DOSE (MG.)	TEMP. (DE- GREES F.)	DIAGNOSIS	INITIAL B.P. (MM. HG)	B.P. IN- CREASE (MM. HG)	DURA- TION OF INCREASE (MIN.)	PEAK B.P. (MM. HG)
7	11/17/41	F	18	95	6	99	Pyelitis	106/68	62/22	28	168/90
8	12/14/41	F	21	120	8	98.4	Pyelitis	102/86	53/9	45	155/95
9	12/14/42	F	39	125	10	99.8	Rheumatoid arthritis	106/74	74/36	40	180/110
10	12/21/41	F	30	175	8	99	Gonorrheal arthritis	122/78	54/12	34	176/90
11	12/23/41	F	58	118	8	101.8	Tularemia	104/62	50/23	33	154/85
12	12/28/41	F	28	183	10	100	Gonorrheal arthritis	116/64	34/16	25	150/80
13	1/12/42	M	38	110	8	105	Paresis and malaria	104/56	66/38	24	170/94
14	3/2/42	F	57	138	10	99	Pneumonia	126/70	38/24	33	164/94
15	4/12/42	F	53	90	8	98.6	Rheumatoid arthritis	108/68	56/20	29	164/88

TABLE III
RESPONSE TO PAREDRINE OF PATIENTS WITH INFECTIONS
(TUBERCULOUS INFECTIONS)

RESPONSE TO TUBERCULOUS INFECTIONS											
NO.	DATE	SEX	AGE (YR.)	WEIGHT (LB.)	DOSE (MG.)	TEMP. (DE- GREES F.)	DIAGNOSIS	INITIAL B.P. (MM. HG)	B.P. IN- CREASE (MM. HG)	DURA- TION OF INCREASE (MIN.)	PEAK B.P. (MM. HG)
1	3/ 2/42	F	16	72	6	99	Tuberculous peritonitis	94/66	31/20	41	125/ 86
	3/ 2/42				6			92/66	38/34	52	130/100
16	12/ 3/41	F	25	85	8	99.8	Pulmonary tuberculosis	86/58	42/34	20	96/ 70
17	12/ 8/42	F	30	90	8	98	Pulmonary tuberculosis	76/58	20/12	20	190/100
18	12/26/41	F	29	112	8	98.6	Psoas abscess	125/84	65/16	45	134/ 84
19	1/24/42	M	46	100	8	102	Pulmonary tuberculosis	108/66	26/18	12	158/100
20	2/ 8/42	F	17	120	8	101.8	Pleurisy with effusion	100/66	58/34	37	156/ 98
21	3/30/42	F	14	86	10	98	Pleurisy with effusion	114/70	42/28	15	130/100
22	3/30/42	M	19	104	10	98	Tuberculous peritonitis	108/88	22/12	40	204/100
23	4/19/42	F	34	120	10	98	Pleurisy with effusion	98/72	106/28	36	200/105
24	4/30/42	M	37	135	8	100.6	Pulmonary tuberculosis	114/82	86/23	37	156/ 85
25	5/24/42	M	41	135	10	98	Pulmonary tuberculosis	116/70	40/15		

TABLE IV
RESPONSE TO PAREDRINE BEFORE AND DURING FEVER

CASE	DATE	SEX	AGE (YR.)	WEIGHT (LB.)	DOSE (MG.)	TEMP. (DE- GREES F.)	DIAGNOSIS	INITIAL B.P. (MM. HG)	B.P. IN- CREASE (MM. HG)	DURA- TION OF INCREASE (MIN.)	PEAK B.P. (MM. HG)
9	12/14/42	F	39	125	10	99.8	Rheumatoid arthritis	106/74	74/36	40	180/110
	12/15/42				10	103.6	After typhoid vaccine	94/58	50/36	31	144/94
10	12/21/41	F	30	175	8	99	Gonorrheal arthritis	122/78	54/12	34	176/90
	12/27/41			8	106	100	After typhoid vaccine	124/70	26/10	10	150/80
12	12/28/41	F	28	183	10	100	Gonorrheal arthritis	116/64	34/16	25	150/80
	12/29/41			10	103.5	100	After typhoid vaccine	96/60	64/26	29	160/86
26	12/21/41	M	43	129	8	98.6	Syphilis of central nervous system	86/44	68/22	70	154/66
	12/23/41			8	102	102	After typhoid vaccine	106/54	36/14	36	142/68
27	4/30/42	M	57	125	8	98.6	Syphilis of central nervous system	112/76	48/18	29	160/94
	5/24/42			8	105	105	After malarial chill	120/68	28/8	21	148/76
	5/25/42			8	98.8	98.8		102/70	38/18	23	140/88

16, 17, 19, 20, 22). In three of the five, the increase in systolic pressure was less than 30 mm. (Cases 17, 19, 22). The initial heart rate in all five patients was more than 100 beats per minute, and these were the only cases in which the pulse rate increased after injection of paredrine. In three of the remaining tuberculous patients, the systolic blood pressure increase was less than the smallest increase observed in the control series, i.e., 48 mm. (Cases 1, 21, 25). Three of the tuberculous patients showed a marked pressor response to the intravenous injection of paredrine (Cases 18, 23, 24).

Fever.—In two of the patients with fever produced by typhoid vaccine (Cases 9, 10, Table IV), the injection of paredrine produced a smaller rise in systolic pressure than during an afebrile period. The duration of the blood pressure elevation was shorter in both of these patients during fever. In a third patient (Case 26) the response was less after a chill than in the control period, but a higher initial pressure made the change somewhat difficult to interpret. In Case 27, the response of the blood pressure to the injection of paredrine was less in the febrile period after a malarial chill than it had been before inoculation with malaria, but did not differ strikingly from the response on the subsequent day, after the temperature had returned to normal. In one patient (Case 12), paredrine produced a greater rise in blood pressure during fever produced by typhoid vaccine than in the pretreatment trial.

Electrocardiographic Observations.—Increase in the height of the T wave in one or more leads was observed in eleven patients (Cases 1, 2, 3, 4, 5, 6, 15, 21, 23, 24, 27). Only three of the thirteen patients whose electrocardiograms were studied failed to show a change in P waves or P-R interval (Cases 3, 22, 27). In two of these a good pressor response to paredrine occurred (Cases 3, 27), but the blood pressure increase in Case 22 was small. In two patients (Cases 1 and 6, Fig. 1), the site of impulse formation changed so frequently that a diagnosis of wandering pacemaker seemed justified, although the ventricular rhythm remained fairly regular in one (Case 6). In one subject (Case 4, Fig. 2), the injection of paredrine was followed by a gross irregularity, with impulse formation shifting between the auricle, A-V node, and ventricle. In three patients (Cases 21, 23, and 28), inversion of the P waves in one or more leads, with shortening of the P-R interval to 0.12 second or less, was noted (Fig. 3). These patients were thought to have auriculoventricular nodal rhythm. In three of the remaining patients, a change in the duration of the P-R interval (Case 2), or less change in both P-R interval and P wave (Cases 5 and 24), was noted. It was felt that these changes were probably due to ectopic impulse formation. The maximum duration of the arrhythmia in any of the above cases was thirty-five minutes. T-wave changes usually persisted until blood pressure and pulse rate returned to the control level.

In Case 15 (Fig. 4) there appeared to be a spontaneous variation in the form of the P wave. On April 12, the patient's control electro-

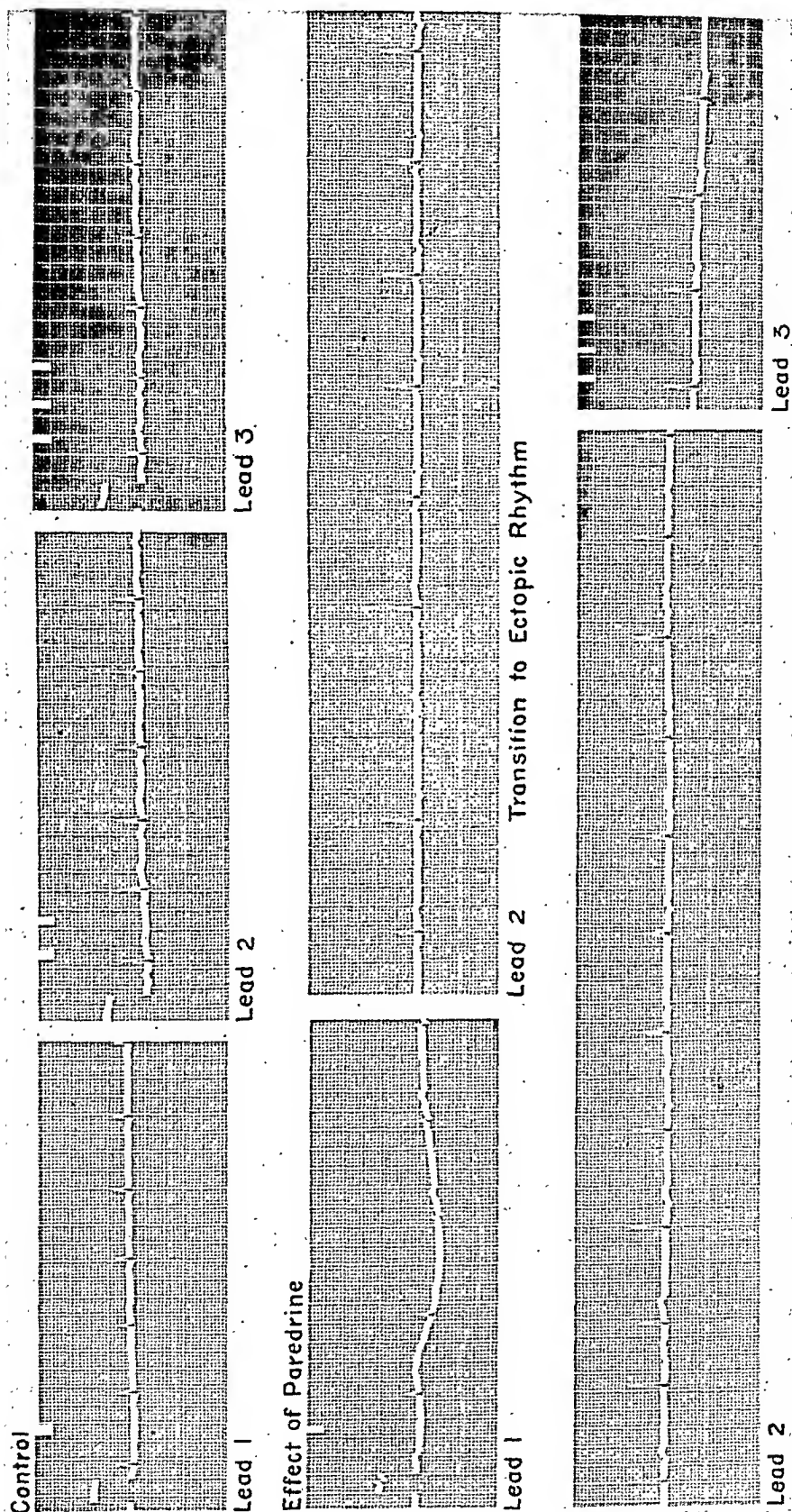


Fig. 1.—Case 6. Wandering pacemaker (possibly parasystole) after intravenous injection of 10 mg. of paredrine, B. P. 190/110. Leads I and II, several minutes after injection of paredrine, show alternation between sinus rhythm and an ectopic rhythm with changed QRS complexes and T waves. The QRS complexes in Lead II show no constant time relation to the P waves, which occur at irregular intervals. The ventricular rate decreases markedly, but remains almost regular. Lead III shows nodal rhythm with a very short P-R interval and ventricular complexes differing from the control tracing. A tracing (not illustrated), taken nineteen minutes after the injection of the drug, showed return to sinus rhythm, with QRS complexes resembling the control, but with higher T waves in all leads. The T waves in the electrocardiogram taken after sixty minutes were the same as in the control strip.

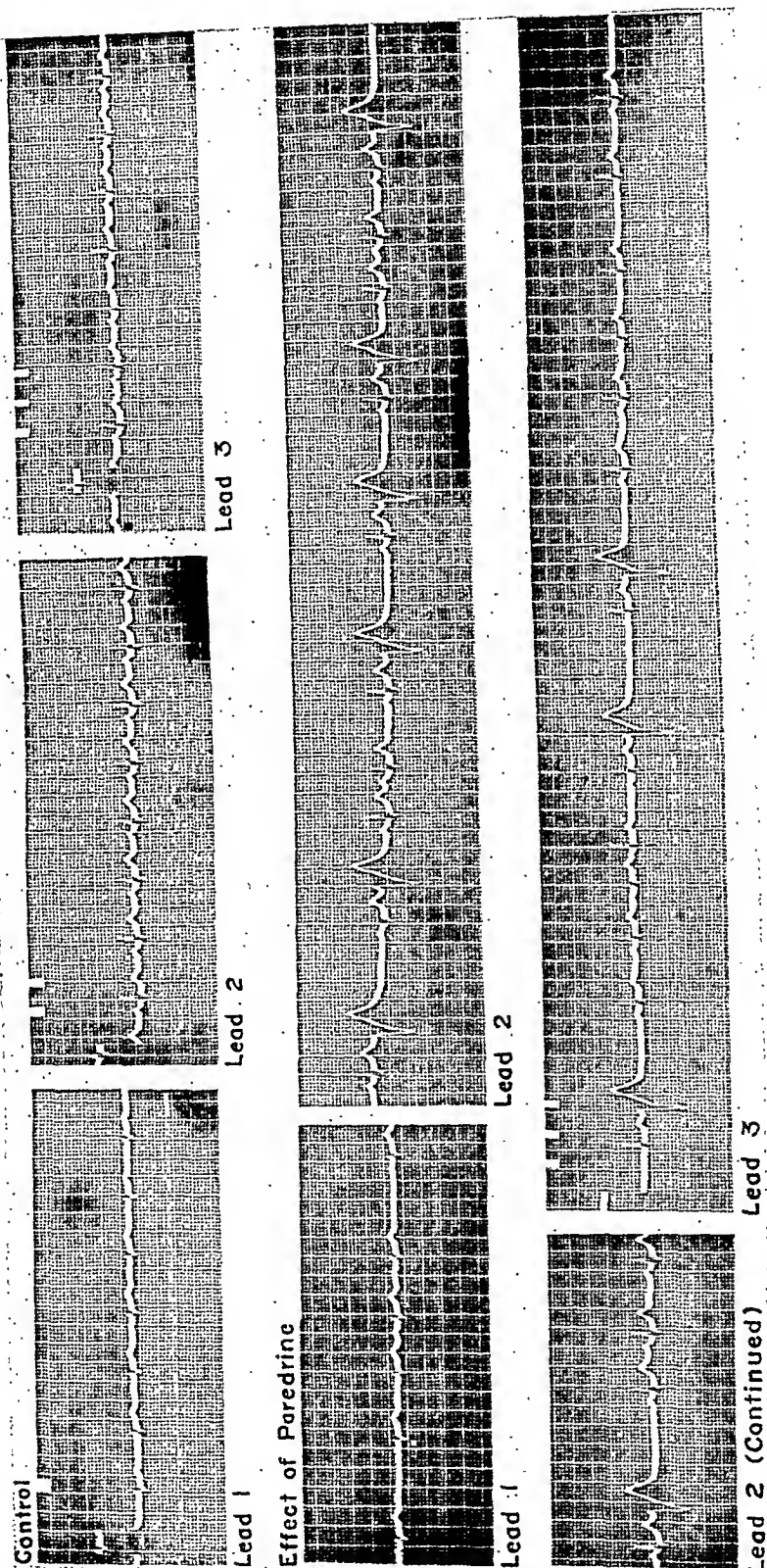


FIG. 2.—Case 4. Grossly irregular rhythm after 10 mg. of paredrine, B. P. 190/105. Leads I, II, and III, taken three minutes after injection of paredrine, show extrasystoles from multiple foci—auricular, nodal, and ventricular. The T waves of the sinus beats are somewhat higher in all three leads. A tracing (not illustrated), taken sixteen minutes after giving the drug, showed sinus rhythm with high T waves. The tracing taken sixty minutes after giving paredrine was identical with the control.

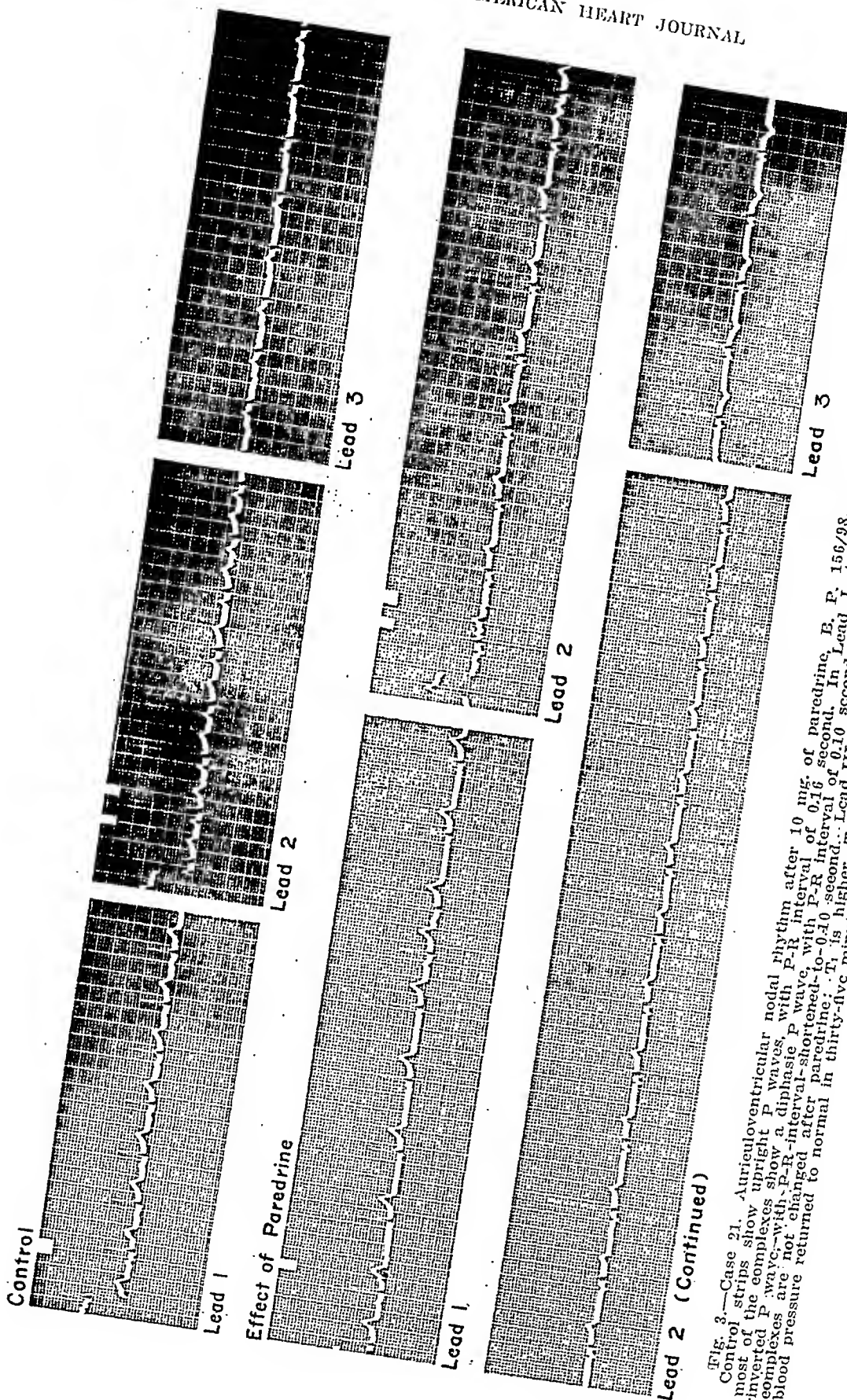


Fig. 3.—Case 21. Auriculoventricular nodal rhythm after 10 mg. of paredrine, E. P. 156/98. Control strips show upright P waves, with P-R interval of 0.16 second. In Lead I, taken three minutes after injecting paredrine, most of the complexes show a diphasic P wave, with P-R interval of 0.10 second. In Lead II, all complexes except one show a sharply inverted P wave, with P-R interval of 0.10 second. In Lead III, also shows inverted P wave and short P-R interval. The QRS complexes are not changed after paredrine; T_1 is higher, T_2 unchanged, and T_3 more sharply inverted. The electrocardiogram and blood pressure returned to normal in thirty-five minutes.

cardiogram showed low P waves, with a P-R interval of 0.12 second. The intravenous administration of paredrine produced a marked increase in the height, and a change in the shape, of the P wave in Leads II and III; these persisted for several hours. By the following day, the tracing had resumed its original form. On April 17, before the administration of any drug, the electrocardiogram showed P waves

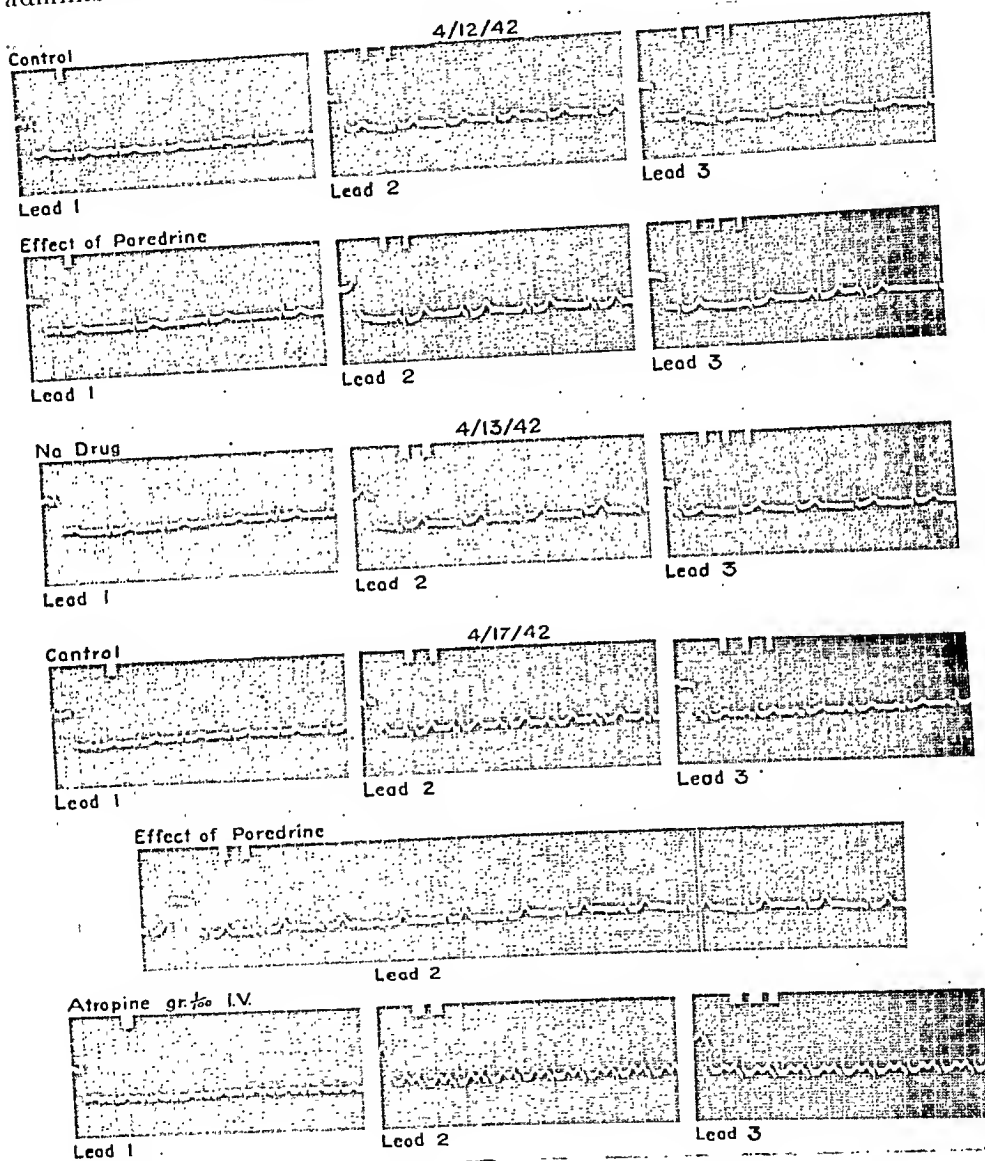


Fig. 4.—Case 15. Changes in P waves spontaneously and after injection of paredrine and atropine.

Control tracing on April 12, 1942 shows rather low P waves in all leads, P-R interval 0.12 second. After injection of 8 mg. of paredrine intravenously (B. P. 164/88), the P waves become higher. Lead III shows examples of both types of P wave. By the next day (April 13) the electrocardiogram had resumed its original form. The control tracing of April 17 appears identical with the tracing obtained after paredrine in the previous experiment. After injection of paredrine, low P waves are noted in Lead II. A moment later, after injection of atropine, the P waves again become high. An electrocardiogram taken three days later (not illustrated) showed high P waves with P-R interval of 0.14 second.

TABLE V

CASE	DATE	SEX	WEIGHT (LB.)	DOSE (MG.)	TEMP. (DEGREES F.)	DIAGNOSIS	INIT. R.P. (MM. HG)	PEAK R.P. (MM. HG)	INITIAL PULSE		ALTERATION IN ELECTROCARDIOGRAM AFTER PAREDRINE
									PULSE RATE PER MINUTE	AT PEAK PER MINUTE	
1	3/2/42	F	72	6	99	Tuberculous peritonitis	92/66	130/100	120	75	Wandering pacemaker. QRS complex unchanged, T waves higher. Return to initial form in 20 min.
2	5/25/42	M	150	10	98.6	General paresis	120/90	216/118	68	57	P-R interval shortened from 0.18 to 0.12 sec., without change in form of P wave or QRS complex. T waves higher, Leads I, II, III. Rhythm regular. Return to initial form in 17 min.
3	5/31/42	M	130	8	97.6	Syphilis of central nervous system	94/60	150/94	94	70	Decrease in rate only significant change
4	6/14/42	M	140	10	98.6	Syphilis of central nervous system	126/84	190/105	95	Irregular	Grossly irregular rhythm with beats from varying foci (see Fig. 2)
5	6/15/42	M	125	8	98.6	Pneumonia (convalescent)	116/68	165/85	90	60	Regular ventricular rhythm, with higher P waves, and P-R interval changed from 0.16 to 0.12 sec. QRS complex unchanged, T waves higher. Rhythm normal in 18 min., T waves at initial level in 40 min.
6	6/21/42	M	145	10	98.6	Gonorrheal arthritis (convalescent)	106/64	190/110	75	60	Nodal rhythm with marked variation in P-R interval (see Fig. 1)

	15	21	22	23	24	27	28
Date	4/12/42	3/30/42	3/30/42	4/19/42	4/30/42	4/30/42	4/ 4/42
Sex	F	F	M	F	M	M	F
Age	90	86	104	120	135	125	90
Temp	98.6	98	98	98	100.6	98.6	100
Diagnosis	Rheumatoid arthritis	Pleurisy with effusion	Tuberculous peritonitis	Pleurisy with effusion	Pulmonary tuberculosis	Syphilis of central nervous system	Cancer of cervix uteri
ECG	8	10	10	10	8	8	8
ECG	108/68	114/70	108/88	98/72	114/82	112/76	118/84
ECG	164/88	156/98	130/100	204/100	200/105	160/94	178/110
ECG	90	100	120	86	96	84	100
ECG	60	75	136	55	80	84	80
ECG	Variation in form of P waves after paroxysmal and spontaneous (see Fig. 4 and discussion in text)	Inversion of P in all three leads, with shortening of P-R interval from 0.16 to 0.10 sec. (see Fig. 3)	Increase in rate only definite change	Inversion of P wave in Leads II and III, with shortening of P-R interval from 0.16 to 0.12 sec. Slight arrhythmia due to irregular occurrence of complexes with upright P waves. QRS unchanged, T ₁ and T ₂ higher. Return to initial form in 35 min.	P waves much higher in Leads II and III, with shortening of P-R interval from 0.16 to 0.13 sec. Increased amplitude of QRS complex and T waves. Return to initial form in 30 min.	T waves higher in all three leads. QRS complexes and rate unchanged	Change in form of P ₁ and P ₂ , inversion of P ₃ . P-R interval shortened from 0.15 to 0.12 sec. QRS complexes unchanged, T waves higher. Return to initial form in 15 min.

identical with those on April 12 after the administration of paredrine. A few minutes after the injection of 6 mg. of paredrine, the P waves again appeared low, as they had in the first electrocardiogram, sixteen days before. Atropine ($\frac{1}{100}$ grain) was given intravenously while the blood pressure remained elevated, and, after about one minute, the P waves returned to the high form. The P-R interval remained at 0.12 second throughout both these experiments. An electrocardiogram three days later showed high P waves, with a P-R interval of 0.14 second.

DISCUSSION

The present study confirms previous observations that the injection of paredrine usually produces no discomfort. The moderate respiratory distress, which occurred in some of our patients has not been noted previously. The constant response of normal subjects to the same amount of the drug is at variance with the observations of Kunkel, Stead, and Weiss;⁸ these authors found that the pressor response after the intramuscular injection of paredrinol was quite variable in the same subject. The increase in blood pressure in the control group and in the majority of the ill patients agreed fairly well with the results of previous investigations of the effect of the intravenous injection of paredrine.^{2, 4}

The adequate and prolonged pressor response to the injection of paredrine in the course of acute infections indicates that a decreased response to paredrine in medical shock is not dependent on the presence of infection alone. This is borne out by observations made in Case 11. This patient showed a marked pressor response to the intravenous injection of paredrine when her blood pressure was normal. Seventeen days later, when her blood pressure had dropped to 50/20 and signs of shock were present, the intravenous injection of 20 mg. of paredrine produced a brief elevation of blood pressure to 110/60, but subsequent, large doses had little effect. Kunkel, et al.,⁸ observed a similar "tachyphylactic" response to paredrinol in medical shock. The present study failed to suggest a reason for the diminished response to paredrine in shocklike states associated with severe infections, nor did it help to explain the mechanism of the vasomotor collapse.

The relatively small pressor response to the injection of paredrine in some of the tuberculous patients was quite clear-cut. In general, the least response was observed in the most emaciated and ill patients, but did not depend on the degree of temperature elevation at the time of the test. It is interesting that the coexistence of pulmonary tuberculosis and hypertension is said to be uncommon.⁹ The reason for the small response to paredrine in this group of patients is not evident. The absence of cardiac slowing was interpreted as a result of the failure of hypertension to develop.

Fever did not influence the pressor activity of paredrine in any of the experiments designed to test its effect, and several of the subjects

with acute infections and high fever showed a good response to paredrine. The decrease in response to paredrine during fever in several of the subjects was probably due to the vasodilatation usually associated with febrile states. Chasis, et al.,¹⁰ observed that the injection of pyrogenic materials produces a fall in the blood pressure of hypertensive subjects, and Goldblatt, et al.,¹¹ believe that a favorable response to depressor substances in hypertension may be related to the appearance of fever.

Abnormal rhythms after the intravenous injection of paredrine in man were not noted by Loman, et al.,² or by Iglauer and Altshule;⁴ neither group made electrocardiographic studies. An increase in height of T waves without change in rhythm has been noted previously in normal subjects after the oral administration of paredrine.¹²

Abbott and Henry¹ reported "extra-systoles and coupling of the beats" after the oral and intramuscular administration of paredrine, but did not discuss electrocardiographic observations. American observers have likewise failed to comment on arrhythmia after the administration of paredrinol. European authors, however, have reported changes in rhythm after the injection of paredrinol (veritol); these included nodal rhythm, extrasystoles, parasystole, interference dissociation, and complete A-V dissociation.^{13, 14}

Keys and Violante, in a recent article,¹⁵ report complete A-V dissociation and changes in P waves in human subjects after the injection of neosynephrin, a substance whose mode of action appears to be similar to that of paredrine. The same authors reproduce an electrocardiogram showing inversion of the P wave and shortening of the P-R interval after the injection of 10 mg. of synephrin tartrate subcutaneously.¹⁶ These changes resemble those interpreted in the present study as indicating A-V nodal rhythm. Adrenalin has also been found to produce ventricular premature contractions and changes in the P wave and P-R interval in man.¹⁷

The production of arrhythmia by paredrine may be related to the occurrence of hypertension rather than to a direct effect on the heart, for it seems to occur only when hypertension is produced. Vagal depressor reflexes, mediated through the carotid sinus or aortic depressor mechanisms, probably cause the cardiac slowing which occurs during hypertension produced by paredrine, for the decrease in rate may be prevented or abolished by atropine⁴ (Case 15). The electrocardiographic changes which are observed in most of the patients, i.e., nodal rhythm, wandering pacemaker, and slow rate, are thought to be due to vagal stimulation.¹⁸ Arrhythmias which occur after the intravenous administration of paredrine have been found to disappear within two to three minutes after the injection of 0.65 mg. of atropine intravenously.¹² The occurrence of transient arrhythmias after the intravenous injection of paredrine need not be considered a contraindication

to the therapeutic use of this compound, for the rhythms encountered do not interfere markedly with cardiac function, nor are they of the type which might be considered as precursors either of ventricular fibrillation or cardiac arrest.

SUMMARY AND CONCLUSION

1. The effect of the intravenous injection of paredrine on the cardiovascular system has been studied in twenty-eight subjects; these included patients with infections, patients with fever produced for therapeutic purposes, and a control group.
2. Intravenous doses of 6 to 10 mg. did not cause severe discomfort or untoward reaction.
3. In nine patients with infections other than tuberculosis, paredrine produced a marked pressor response. Three of the eleven tuberculous patients showed a much smaller pressor response, and five other patients of this group had only a moderate or shortened pressor response to paredrine.
4. Four patients were studied before and during fever produced by the injection of typhoid vaccine; three showed a smaller response during fever. In one patient with malaria the pressor response was moderately diminished during a febrile period.
5. Changes in cardiac rhythm appeared frequently. The electrocardiogram showed wandering of the pacemaker in three subjects. Ectopic rhythms, probably originating in the auriculoventricular node, were observed in seven subjects. The arrhythmias were attributed to reflex vagal stimulation.
6. The cause of the relatively slight pressor response to paredrine in some of the patients of the present series is not apparent.

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Clinical Reports

THE ELECTROCARDIOGRAPHIC MANIFESTATIONS OF EARLY ACUTE COR PULMONALE

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THE electrocardiographic changes associated with pulmonary embolism represent, in the main, the effects of suddenly produced, acute, right ventricular strain. These changes conform to well-established trends of electrocardiographic behavior. Thus, a prominent S wave in Lead I, an R wave in Lead III (expressing, in reality, right axis deviation), an inverted T wave and a deep Q wave in Lead III, a small or isoelectric T wave in Lead II (rarely inverted), arising from an S-T segment that has an isoelectric or depressed S-T junction, and inversion of the T waves in precordial leads taken at the C₂ position and at times in precordial leads obtained from position IV, have become well-recognized criteria of pulmonary embolism. When the T waves obtained in the C₂ position are negative, and, at the same time, the T waves obtained at position IV are positive, the evidence is specific for acute right ventricular strain, usually due to pulmonary embolism. It should be emphasized, however, that the electrocardiographic diagnosis of pulmonary embolism should depend on the pattern of changes observed in all the leads, rather than isolated electrocardiographic changes.

A noteworthy feature of the electrocardiographic changes associated with pulmonary embolism is their temporary nature. This would be accounted for most satisfactorily if it could be proved that an embolus in a pulmonary artery leads to transitory vasospastic phenomena throughout the pulmonary arterial tree, and there is some reason to believe that this is what occurs.^{1, 2} It is to be expected, therefore, that the most marked electrocardiographic changes will be present shortly after the occurrence of embolism, and that a gradual trend toward normal will follow if the patient survives the attack.

One of the early changes which has not been stressed in all reports (although reproductions of some electrocardiograms^{3, 4} show it) is a marked widening and slurring of the S wave in Lead I or Leads I and II which closely resemble the type of bundle branch block that is reputedly due to a conduction disturbance in the right bundle branch.

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In one of Pick's cases the curve was of this type.⁵ In this case an electrocardiogram was made immediately after the occurrence of pulmonary embolism.

Furthermore, Durant, Ginsberg, and Roesler⁶ reported three cases of pulmonary embolism in which electrocardiograms made soon after the onset of symptoms showed delayed intraventricular conduction of the right bundle branch type, with a broad, shallow S wave in Leads I and II, and marked depression of the S-T segments in these leads. Within five to twelve hours after the onset of the pulmonary embolism, the bundle branch block had disappeared, leaving depressed S-T segments and a "staircase" type of ascent to the T wave.

We wish to report a case which illustrates the early electrocardiographic manifestations of pulmonary embolism unusually well. In this case we were fortunate enough to obtain a record immediately after an attack of pulmonary embolism which proved fatal shortly afterward.

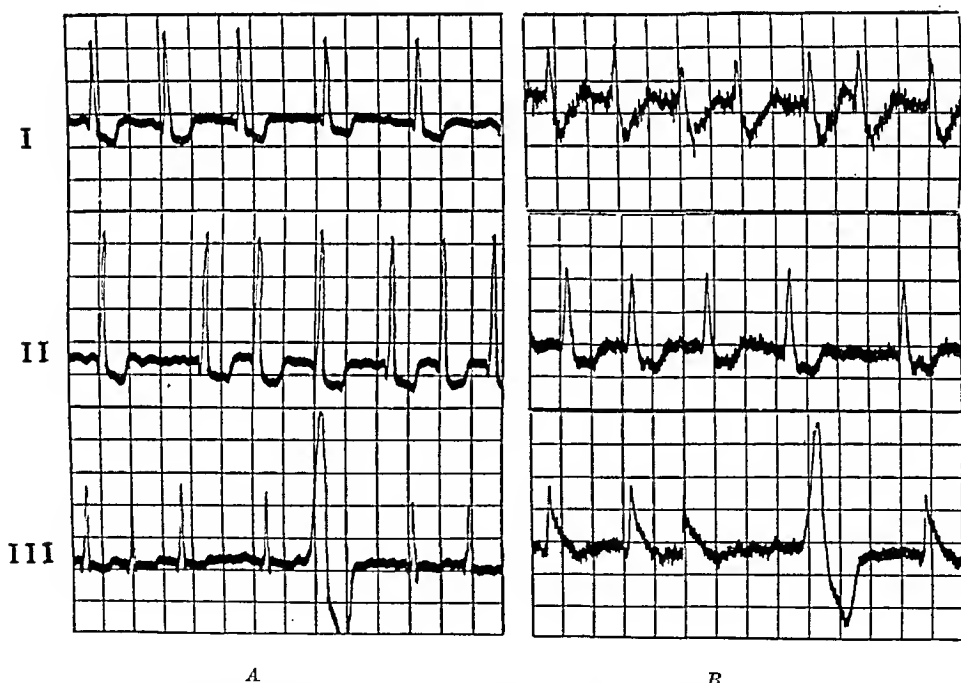


Fig. 1.—A, Electrocardiogram made on admission of patient; note the depressed S-T segments in Leads I and II, with inverted T waves in these leads (effect of digitalis); B, record made five minutes after the occurrence of pulmonary embolism. Bundle branch block, with a wide S wave in Leads I and II and S-T segment depression in these leads.

REPORT OF CASE

The patient was an obese woman, 64 years old. Two months before admission she had been awakened by a fluttering sensation around her heart. In the light of subsequent observations this probably indicated the onset of auricular fibrillation. She also had begun to notice a considerable degree of weakness. Digitalis had been prescribed by her family physician, but the response was not very satisfactory.

On admission, she had symptoms of mild congestive heart failure. The blood pressure was about 200/110. There was definite cardiac enlargement. The auricles

were fibrillating and the ventricular rate was 164 beats per minute. Hyperthyroidism was suspected because of the rapid ventricular rate, muscular weakness, moderate intolerance of heat, and a small adenoma of the left lobe of the thyroid gland. She had, in addition, an afternoon temperature of about 100° F. (37.7° C.). Under these circumstances accurate measurement of the basal metabolic rate was impossible, and definite exclusion of hyperthyroidism was therefore difficult.

We were unable to ascertain from the patient's history how much digitalis she had taken prior to admission, but the electrocardiogram revealed marked changes in the S-T segment of the type which is common after digitalization of a patient with a condition producing strain of the left ventricle (Fig. 1A).

The patient was hospitalized for further observation and treatment. On the fourth day, pain developed, pleuritic in character, in the left side of the thorax. This was followed three days later by the coughing up of bloody sputum, so that it was quite apparent that she had pulmonary embolism. Her condition was improving satisfactorily until two weeks later, when she suddenly became weak and complained of pressure over her chest. She was gasping for breath and showed signs of shock. An electrocardiogram was made immediately. She died about ten minutes later.

This electrocardiogram (Fig. 1B) showed marked changes as compared with the former one. The changes consisted essentially of a widening of the QRS complexes. It is to be noted that this was caused by a markedly slurred and widened S wave. At necropsy the heart was found to be enlarged, and weighed 580 grams. A moderate degree of sclerosis existed throughout the coronary tree, although it was more marked in the descending branch of the left coronary artery. There was no cardiac infarction. Fresh emboli were present in both pulmonary arteries, and there were old infarcts in the left lung, with overlying pleuritis. There was extensive thrombus formation in the femoral and iliac veins. The nodule in the left lobe of the thyroid gland was found, on microscopic examination, to be merely a fetal adenoma.

COMMENT

If it can be said that there is a type of person who might be expected to have pulmonary embolism, this patient conformed to that type. She was obese, and a factor favoring venous stasis and the formation of thrombi, namely, congestive heart failure, was present. The frequency with which one attack of pulmonary embolism is likely to be followed by another is also well illustrated in this case.

The extensive thrombus formation in the femoral and iliac veins is worthy of note. Very frequently it is assumed that the source of pulmonary emboli among patients whose auricles are fibrillating is the right auricle. Although this must be true in some cases, it is more than likely that in most instances the emboli originate in the peripheral venous system.

The electrocardiogram which was made within five minutes of the occurrence of the pulmonary embolism showed an abnormality of the QRS complex of the type which has been observed after experimental pulmonary embolism⁶ and also after experimental section of the right bundle branch.⁷ It is possible that digitalis may have contributed to these changes.

This record further resembles the type of ventricular conduction disturbance which has been designated as the "wide S-wave pattern," and

is believed to represent right bundle branch block.⁸ This is most commonly associated with coronary sclerosis, and is a permanent rather than a transitory state.

Considerable evidence⁹⁻¹¹ is available to show that among patients who have a wide S-wave pattern there is an asynchronism between the beats of the two ventricles, and the left contracts before the right. In the presence of pulmonary embolism the right ventricle is suddenly subjected to a tremendously increased load (acute right ventricular strain), apparently caused in part by reflex spasm of the entire pulmonary arterial bed.^{2, 12, 13} Among patients who survive, the right ventricle rapidly dilates and is at first unable to cope efficiently with this resistance. Asynchronism of the two ventricles can readily be accounted for by such a disturbance. It is at this stage that the electrocardiographic picture of delayed intraventricular conduction, resembling one type of right bundle branch block, is seen.

The possibility that a reflex constriction occurs in the coronary arterial tree also has been postulated to explain the electrocardiographic characteristics of pulmonary embolism. This concept has received considerable support from the results of experiments which have revealed the presence of sensitive vasoreceptors in and around the pleura,¹⁴ bronchi,¹⁵ and pulmonary arteries,^{16, 17} the stimulation of which produced widespread reflex changes, some of which suggested coronary constriction. De Takats and his co-workers¹⁸ obtained electrocardiograms from dogs after the production of experimental pulmonary embolism, and they were of the type which indicates interference with the coronary circulation. Clinical evidence, aside from electrocardiographic phenomena, that pulmonary embolism may produce coronary artery spasm is derived mainly from reports of cases in which only small portions of the lung were infarcted, but in which the outcome nevertheless was fatal.

Friedberg and Horn¹⁹ reported that twelve instances of myocardial infarction *without* coronary occlusion were found in cases of pulmonary embolism in which the outcome was fatal. This would constitute certain evidence in favor of the theory of reflex production of coronary artery spasm, were it not for the fact that four of their patients had angina, four had hypertension, and three had symptoms of congestive heart failure, in all of which cardiac infarction may occur without demonstrable coronary artery occlusion.

SUMMARY

A case is presented which demonstrates the early electrocardiographic manifestations of acute cor pulmonale. The characteristic abnormality at this stage is a wide, slurred S wave, especially in Lead I. This widening of the S wave tends to recede after a few hours, and the electrocardiographic pattern then becomes the same as that previously described

as typical of pulmonary embolism. The physiologic basis for these changes is discussed.

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CORONARY THROMBOSIS AND MYOCARDIAL INFARCTION IN YOUTH

REPORT OF A CASE, WITH AUTOPSY, IN A 19-YEAR-OLD MALE

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SINCE the classical clinical descriptions of coronary thrombosis by Obratzow and Strascheko,¹ in 1910, and by Herrick,² in 1912, the clinical diagnosis of this disease has been made with increasing frequency and accuracy. Although coronary thrombosis is ordinarily regarded as a disease of late middle life (45 to 60 years), recent reports have shown that it occurs occasionally in persons under 20 years of age.

A review of the literature disclosed eight cases^{3a-5*} of coronary thrombosis between the ages of 10 and 20 years. In six of these the diagnosis was confirmed by autopsy, and in two cases^{3b} the diagnosis rested upon clinical evidence alone. Review of the literature also revealed five cases^{4a-c} of medial coronary sclerosis in infants from birth to 27 months, in which evidence of myocardial damage (presumably infarction) was present.

It is of interest that, during the past decade, the literature contains an ever increasing number of references to the incidence of coronary thrombosis among persons between 25 and 40 years of age.^{5a-b} Whether this apparent increase in incidence is real or dependent upon our changing mode of life, or whether it is due to improved clinical acumen and lack of hesitancy upon the part of the clinician to make the diagnosis in youth is beyond the scope of the present report.

Although the case to be reported offered no problem in clinical diagnosis (because of the classical history and characteristic manifestations), yet because of the patient's age and the opportunity to corroborate the diagnosis post mortem, this case is added to the group of eight patients from 10 to 20 years of age who have been reported.

CASE REPORT

History.—D. B., a 19-year-old Jewish boy, was admitted to the Jewish General Hospital for the first time on April 18, 1941, to the medical service of Dr. H. N. Segall, with a history of precordial pain upon exertion, of one year's duration. This pain was accompanied by a feeling of oppression, and radiated to the epigastrium, left shoulder, and down the left arm, and was relieved by one to two hours' rest. These attacks would come on at work or upon hurried walking. Upon more detailed questioning he admitted that these symptoms first commenced in the

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*The cases of Huchard, mentioned in Allbutt and Rolleston's *System of Medicine*, Vol. 6, p. 172, 1909, are not included because of inability to obtain the original reference.

autumn of 1937. At that time, however, they were infrequent, and of such a mild, transitory nature that he dismissed them as being inconsequential. In the preceding year the pains had increased both in frequency and severity, and, upon one occasion, he sought the advice of his family physician, who suggested a thorough checkup. The patient disregarded this advice.

On the morning of admission, while at work, he experienced a sensation of dizziness and decided to go home. As he mounted the streetcar, he was suddenly seized with severe precordial oppressive pain, which radiated to the left shoulder and arm and was not relieved by rest as it had been in the past. He left the streetcar and could not continue homeward. He sat down on a doorstep, called a cab, and presented himself at the hospital for admission.

The patient worked as a shipper, and did moderately heavy manual labor. He had smoked about twenty-five cigarettes a day until three months before, at which time he cut his consumption to five or ten cigarettes a day. His past history revealed only occasional, postprandial, right upper quadrant distress after the ingestion of fatty or fried foods, occasional headaches and dizziness, and infrequent pains in the knee joints.

His mother had hypertension, with a blood pressure of 170/100, and electrocardiographic evidence of myocardial disease. There was no other family history of cardiovascular disease.

Physical Examination.—The patient was a healthy looking, well-developed, and well-nourished white boy who was in some distress as he lay in the dorsal recumbent position.

The heart was not enlarged to percussion. There was a loud systolic murmur at the apex. The pulmonic second sound was louder than the aortic second sound. The blood pressure was 142/86. There was a questionable respiratory lag of the right side of the chest, with many fine, moist râles over the lower half of the right side and a few at the left base. The rest of the examination was negative.

Laboratory and Special Clinical Examination.—Urinalysis, negative. Erythrocyte count, 5,150,000; hemoglobin, 102 per cent; leucocyte count, 14,000; differential count: polymorphonuclear leucocytes, 78 per cent, lymphocytes, 17 per cent, monocytes, 3 per cent, eosinophiles, 2 per cent.

The electrocardiogram was remarkably abnormal; it showed slurred QRS complexes in all leads, and depressed S-T segments in Leads I, II, and III, suggesting recent myocardial infarction.

A roentgenogram of the chest showed pulmonary congestion.

Progress.—His course in the hospital was brief. Morphine afforded slight relief from pain, and the patient slept comfortably from midnight to 5:30 A.M., when his condition became very poor. He had an ashen color, was deeply cyanosed, sweated profusely, and had a thready pulse of 120 per minute. His breathing was labored, and he coughed up pink-stained, foamy sputum. The chest was full of râles, the heart sounds were distant, and his blood pressure had fallen to 108/80. Because of this fall in blood pressure, no phlebotomy was performed. He was placed in an oxygen tent and given pantopon. He continued to grow worse, and died one hour later, approximately twenty hours after admission.

The clinical diagnoses were coronary occlusion, myocardial infarction, and acute pulmonary edema.

Autopsy (performed by Dr. M. A. Simon, nine hours after death).—The body was that of a well-developed and well-nourished white man. There was marked cyanosis of the mucous membranes and nail beds, and frothy, bloody fluid exuded from the mouth.

The heart weighed 390 grams, but was of the usual shape. The epicardium was everywhere thin, smooth, and transparent. Over the anterior and lateral aspects

of the apical portion of the left ventricle the small veins were prominent and injected. The myocardium at this point was somewhat more flabby in consistency than elsewhere. The auriculoventricular sulcus was not obliterated. The coronary arteries were straight and pliable to palpation. The left circumflex branch ended on the obtuse margin of the left ventricle, but the right coronary artery crossed the midline posteriorly to supply the posterior aspect of the left ventricle. Upon section, all chambers were of the usual size and shape. The endocardium throughout was smooth and glistening, and no mural thrombi were seen. All of the valves showed thin, delicate, and translucent leaflets in which no anomalies or evidence of gross pathologic change was present.

Section through the lateral aspect of the left ventricle showed a somewhat granular, mottled yellow and red myocardium that was flabby in consistency. On anterior section through the left ventricle, parallel to the interventricular septum, the myocardium showed the same mottled appearance, but, in addition, a few gray, fibrous streaks could be seen in the muscle of the interventricular septum.

The left coronary orifice was of the usual size and shape, but, upon looking into it from the aorta, the lumen was found to be filled with a loosely adherent, grayish-red blood clot. This recent thrombus completely occluded the common left coronary trunk, and extended into the left circumflex branch for a distance of 5 mm. Beyond the point of occlusion in the left circumflex branch the coronary wall was thin and pliable and the intimal surface was smooth and glistening.

Transverse sections through the left descending ramus showed that the lumen was completely occluded for a distance of 15 mm. beyond its origin by a firmly adherent, mottled red and grey thrombus that differed from the thrombus occluding the common trunk and left circumflex branch. Beyond this region, in the left descending ramus, the lumen was empty. The walls were thin and pliable and the intimal surface was smooth and glistening.

The right coronary orifice was of the usual size and shape and was not occluded. Section revealed thin, pliable walls, and an occasional, tiny, yellow intimal plaque which did appear to reduce the caliber of the lumen. The right coronary artery coursed beyond the midline posteriorly, and supplied the posterior aspect of the left ventricle.

The aorta showed a few yellow, atheromatous streaks near the orifices of the vertebral arteries. The lungs were the seat of edema and passive hyperemia. All other viscera and the brain showed only passive hyperemia.

Microscopic Examination.—A section taken through the left descending ramus, close to the point of origin, showed complete obliteration of the lumen by a well-organized and canalized thrombus (Fig. 1). The thrombus was composed of granulation tissue, and contained many lymphocytes, occasional plasma cells, and moderate numbers of polymorphonuclear leucocytes. The thrombus contained many endothelial-lined spaces containing erythrocytes, and, within two of these vessels, recent thrombi, showing beginning organization, were present.

The intima of the coronary artery was irregularly thickened, and, in one location, was elevated and composed of lamellated, relatively acellular, fibrous connective tissue containing a few acicular slits. The media was thin and intact throughout, and, in the thickened, fibrous adventitia, a few thick-walled arterioles and capillaries with perivascular collars of lymphocytes were encountered. A section stained by the Weigert method revealed splitting and fragmentation of the internal elastic lamella. The external elastic lamella was intact throughout, and several fine elastic fibers were seen in the media.

A section through the left circumflex artery immediately beyond its point of origin (Fig. 2) showed that the lumen was completely occluded by a recent lamellated thrombus composed of layers of erythrocytes, fibrin, and leucocytes. In one area

this thrombus showed beginning organization. The left circumflex showed irregular intimal thickening, and, at one point, a large, spherical plaque narrowed the lumen in an eccentric fashion. In the lowermost portions of this plaque several focal collections of histiocytes and round cells were seen. The internal elastic lamella showed only slight focal fragmentation. The media was not remarkable.

A section of the interventricular septum taken at right angles to the longitudinal axis of the left descending coronary artery revealed two branches of the descending ramus lying in fat. These were the seat of completely organized and canalized thrombi. In the interventricular septum there were large, irregular, well-vascularized areas of fibrous tissue, which separated and replaced large masses of myocardial fibers. In addition to this change, the deeper portions of the myocardium showed loss of staining quality, with loss and pyknosis of nuclei and a sparse but diffuse infiltration of polymorphonuclear leucocytes.



Fig. 1.



Fig. 2.

Fig. 1.—Section of left descending coronary ramus showing subintimal fibrosis and thrombosis, with canalization and subsequent thrombosis of canalized vessels.

Fig. 2.—Section of left circumflex coronary branch just beyond its origin. Note the marked eccentric subintimal fibrosis of wall and reduction in lumen. The lumen is filled with a recent and lamellated thrombus which was continuous with thrombus plugging the canalized vessels of a remote thrombus in the left descending ramus.

A section through the posterior aspect of the left ventricle revealed marked loss of staining quality of muscle fibers, granularity of cytoplasm, destruction and pyknosis of nuclei, and diffuse interstitial infiltration by large numbers of polymorphonuclear leucocytes. A small amount of interstitial hemorrhage was present.

Sections of the lungs showed pulmonary edema and passive hyperemia. All other sections showed only passive hyperemia.

Anatomic Diagnosis.—Coronary arteriosclerosis; remote coronary thrombosis of left descending ramus, with organization, canalization, and recent, superimposed thrombosis; recent thrombosis of left circumflex branch; remote and recent infarction of interventricular septum; recent infarction of left ventricle; pulmonary edema; hydrothorax, bilateral; chronic passive hyperemia of viscera.

DISCUSSION

The type of coronary arteriosclerosis in this case differed slightly from that of older persons, in that less atheroma and no calcification were

present. The subintimal lesion was fibrous in nature, but the few acicular slits indicated that conversion of cholesterol esters to crystals had occurred. According to Leary,⁶ the characteristic lesion of coronary sclerosis in young persons is fibrosis associated with lipoid cells which do not accumulate in large aggregations because of the growth of fibrous tissue. He is of the opinion that the cause of death in the young is thrombosis secondary to subendothelial necrosis which extends to the endothelium. No distinct subendothelial necrosis could be demonstrated in the present case.

Of the cases of coronary thrombosis between the ages of 5 and 20 years previously reported, adequate microscopic studies are available in only three. Thus, in the cases of Sprague and Orgain^{3a} and of Benda,^{3e} at the ages of 15 and 12 years, respectively, characteristic atherosclerotic changes were present, whereas, in the case reported by Jamieson and Hauser,^{3f} that of an 18-year-old boy, the larger coronary branches showed a purely degenerative arteriosclerosis, with slight calcification, and the smaller branches showed proliferating endarteritis.

In infants between the time of birth and the age of 27 months the coronary artery changes are quite different from the usual sclerotic changes in adults. They consist of medial calcification, with or without intimal thickening, and resemble the changes which occur in experimental animals after overdosage with parathyroid extract⁷ or vitamin D.⁸ No proof is presented in any of the reported cases of coronary sclerosis in infants that overdoses of vitamin D were given, and the cause of these medial changes remains controversial.

The patient in the present case suffered severe anginal attacks for at least one year before death. This is understandable because of the marked reduction in the lumen of, and hence in the blood flow through, the left descending ramus. The thrombus, however, was well canalized, and must have permitted sufficient flow of blood to nourish the interventricular septum until the last attack. It was not until the final thrombus occluded the left circumflex branch, as well as a few of the canalized vessels in the thrombus of the descending ramus, that death occurred. Sections through the interventricular septum showed patchy areas of fibrosis and bland necrosis of the myocardium, but, in addition, a few areas of leucocytic infiltration were seen. Sections from the posterior aspect of the left ventricle showed much more extensive leucocytic infiltration, accompanied by necrosis of the myocardium. These observations suggest that the initial thrombosis of the left descending ramus did not completely occlude this artery, but gradually grew by accretion and became organized and canalized, and that it was not until the final thrombus occluded not only these canalized vessels, but the circumflex branch as well, that death ensued.

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Abstracts and Reviews

Selected Abstracts

Wégria, R., Rojas, A. G., and Wiggers, C. J.: A Study of Spontaneous Fulminant Shock in a Heart-Lung-Dog Preparation. *Am. J. Physiol.* 138: 212, 1943.

The relative importance of (a) decrease in venous pressure and secondary reduction of cardiac output, (b) primary myocardial impairment, and (c) changes in total peripheral resistance (TPR) in shock was studied by means of a heart-lung-dog preparation, which is described. Venous flow and cardiac output were under control, and TPR could be calculated. In such a preparation, a fulminant type of shock develops spontaneously which may resemble clinical types characterized by speedy circulatory failure and death.

In twenty-four such experiments it was shown (a) that shock can develop without progressive reduction or even with a rise of venous pressures or cardiac output, and (b) that it cannot be prevented or cured by increased venous inflow and cardiac output.

The fundamental factor responsible for this type of irreversible circulatory failure was a steady and pronounced decrease in total peripheral resistance, which enabled the animal to store, over and above its own blood volume, quantities of blood equal to 25 per cent of its body weight, or four times its own blood volume. Autopsies revealed no storage depots other than the mucosa of the upper intestines, which was always edematous, intensely congested, and often hemorrhagic. The integration of these observations with apparently contrary findings regarding the state of the peripheral circulation, and their application to fulminant types of shock in man are discussed.

Following any prolonged period of hypotension during the development of shock, the cardiac output at equivalent venous pressures also decreased, indicating that depression of the myocardium occurred. In the form of shock studied, this did not prove to be an initiating factor nor was it necessary to produce an irreversible state. But, after the peripheral changes of shock had been well established, it played an important role in the rapid downward trend of blood pressure and was the ultimate cause of death.

Five dogs, primed with liberal doses of cortical adrenal extracts, and receiving these extracts during the experiments, revealed no indications that the course of dynamic events or the pathologic changes in the intestinal mucosa were influenced. It must be recognized, however, that the authors' preparations perhaps offered too severe a test.

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Simister, T. H., and Conklin, R. E.: The Role of Pressoreceptors in the Regulation of Blood Pressure in the Rabbit. *Am. J. Physiol.* 138: 391, 1943.

Brief tipping experiments have been done on thirty-two rabbits, with progressive elimination of sources of afferent impulses causing reflex circulatory compensation. It has been shown that the rabbit is still able to compensate to some extent for the effect of gravity when it is deprived of vagi, aortic nerves, carotid sinuses and splanchnic nerves. Some other reflexogenic sources, responsible for the compensation, must exist.

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Ponder, E., and Hyman, C.: The Cytologic Effect of Saponin on the Walls of Vessels. *Am. J. Physiol.* 138: 432, 1943.

When frog muscle is perfused with saponin or bile salts in frog Ringer, the permeability of the vessel walls is increased, and this results in an increased rate of edema formation. If the muscle is perfused with a solution of hemoglobin to which saponin or bile salts have been added, the hemoglobin, which in the absence of the lysins, remains in the vessels, escapes through the vessel walls and appears in the extravascular spaces. While these effects are being produced, the lysins disappear, in part, from the perfusion fluid, being taken up by the vessel walls and other tissue cells. Quantitative determinations of the rate of uptake of the lysins, and of their effects on permeability, show that the kinetics of the cytolytic process are similar to the kinetics of hemolytic processes. The quantities of saponin involved in producing these changes in permeability are such as would cover the walls of the vascular system of the muscle with a layer of lysin less than ten molecules thick.

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Bernstein, S. S., and Ginzburg, L.: Status Anginosus Due to Profound Anemia. *J. Mt. Sinai Hosp.* 9: 142, 1942.

Angina pectoris of increasing severity appeared in a 62-year-old man suffering with profound anemia due to two independent gastrointestinal neoplasms. The cardiac pain was promptly relieved following transfusions, and never recurred after two operative procedures, even with the resumption of full activity.

KERSHBAUM.

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Graybiel, A.: Some Problems in Aviation Medicine. *J. Lab. & Clin. Med.* 28: 590, 1943.

Dill, D. B.: Physiology of Fatigue: Factors and Criteria of Endurance. *J. Lab. & Clin. Med.* 28: 596, 1943.

These three lectures were part of a series given at the Metropolitan State Hospital, Waltham, Mass. The authors discuss the general problems involved in aviation medicine, particularly the response of the heart and circulation to abnormal conditions of flying. Much of the material is the application of studies on fatigue made by the authors. The lectures are of value to the cardiologists who may find themselves engaged in aviation war medicine.

McCULLOCH.

Lewis, T.: Swelling of the Human Limbs in Response to Immersion in Cold Water. *Clin. Sc.* 4: 349, 1942.

When an extremity is cooled, as by immersion in cold water (5° C.), it swells. This increase of volume occurs in both skin and subcutaneous tissue, and within three hours may amount to as much as 15 per cent of the original volume.

The swelling is due mainly to an edema of the tissues, judged to be inflammatory from its relatively rapid outpouring and from its relatively high protein content. The contribution in the form of imbibed water is very slight.

From this and correlated evidence, it seems that cold directly injures the skin and subcutaneous tissues. This effect begins at about 15° to 18° C. and increases as the scale of temperature is descended.

The production of edema as a result of long-continued immersion of the limbs in cold water should be taken into account, as should protein loss, in estimating the effects of exposure to cold upon the whole circulation.

AUTHOR.

Wolferth, C. C., Livezey, M. M., and Wood, F. C.: Distribution of the Patterns of Ventricular Potential Which Determine the Forms and Significance of Electrocardiograms. *Am. J. M. Sc.* 205: 469, 1943.

Much of the confusion which now exists in clinical electrocardiography could be eliminated if, in all leads, one of the paired electrodes were attached to an area of relatively slight potential variation, such as the right scapular region. Under such circumstances, an electrocardiogram may be obtained which presents a relatively undistorted record of the potential variations of the exploring electrode. From data now available, it is possible to say that the exploring electrode should be placed on a number of chest positions such as C_1 to C_6 inclusive, if one wishes to acquaint himself with the chief features of the various patterns which may be formed on the surface of the chest, including the two widely distributed to the upper parts of the trunk and arms. In order to obtain information regarding the pattern widely distributed below the diaphragm, it is necessary to place the exploring electrode on some position at least a few inches below the parietal attachments of the diaphragm. The best position or set of positions for this purpose has not as yet been determined.

AUTHORS.

Nylin, G., and Grewin, K. E.: Three Chest Leads and Their Value in Association With the Leads From the Extremities, and Several Other Chest Leads. *Cardiologia* 6: 169, 1942.

Some of the formerly introduced chest leads, and three, proposed by Nylin, called the longitudinal, the transverse, and the sagittal lead, are described. The importance of an exact localization of the lead off points by means of radioscopy is argued. About 350 heart cases have been examined with the above mentioned leads and part of them with the Nehb, Jervell, and CF_1 leads. The transverse lead is of little value; the longitudinal and the sagittal ones, however, possibly are valuable. The Nehb leads are to be further investigated, since they seem to be valuable especially the dorsal one, for the diagnosis of posterior infarction.

AUTHORS.

Rosenbaum, F. F., Johnston, F. D., and Keller, A. P.: Paroxysmal Ventricular Tachycardia in Childhood. *Am. J. Dis. Child.* 64: 1030, 1942.

A review of the literature has disclosed seven cases of paroxysmal ventricular tachycardia in childhood, which satisfy the criteria necessary for this diagnosis. Two additional cases, recently observed in this clinic, are reported.

The first case was that of a child with congenital heart disease who had had ventricular tachycardia for two weeks. The paroxysm ceased only after a large amount of quinidine was given. For a few days thereafter, the patient exhibited unusual forms of independent auricular and ventricular rhythms, together with alternations in the form of the ventricular complexes.

The second case was that of a boy with no evidence of structural heart disease, who had frequent, symptomless paroxysms of ventricular tachycardia of short duration. The arrhythmia disappeared on exertion.

Measures usually employed in the treatment of supraventricular tachycardia are without effect in ventricular tachycardia, and it is therefore essential to differentiate

these two types of tachycardia whenever a case of paroxysmal rapid heart action of significant duration is encountered. Careful clinical and electrocardiographic studies should be made to determine whether the tachycardia is supraventricular or ventricular in origin, and if it is the latter, quinidine sulfate should be given in adequate dosage to convert the rhythm to normal.

AUTHORS.

Strauss, S., and Langendorf, R.: Bilateral Partial Bundle Branch Block. Am. J. M. Sc. 205: 233, 1943.

A case is reported of sinus rhythm with intraventricular block showing variations of the ventricular complexes between the common and uncommon types. This change is associated with the occurrence of advanced partial A-V block. The alternations are explained by assuming partial block in the two main bundle branch systems, with a shorter relative refractory phase of the bundle branch which has the longer absolute refractory phase.

AUTHORS.

Rhodes, P. H., and Durbin, E.: Coarctation of the Aorta in Childhood: Review of the Literature and Report of Three Cases. Am. J. Dis. Child. 64: 1073, 1942.

A review of the literature on coarctation of the aorta revealed forty-seven cases in which adult type had been diagnosed during life in children under 15 years of age. It is important to make the diagnosis of coarctation as early in childhood as possible, since the life of the patient may be prolonged by prohibiting strenuous sports and occupations.

When coarctation of the aorta is pronounced enough to give clinical signs, its diagnosis is not difficult if the condition is kept in mind. It should be suspected when forceful pulsations in the neck, and hypertension, particularly with a wide pulse pressure, are observed in the child. The presence of a much lower blood pressure in the lower extremities and of retardation and diminution of pulsation in the femoral arteries confirms the diagnosis. The finding of a collateral circulation, and the roentgenologic signs are valuable aids.

If routine determinations of blood pressure in children are made only on one arm, the right arm should be used, in order to avoid overlooking the occasional cases of coarctation in which the pressure is low in the left arm. Such a case is reported, together with interesting electrocardiographic observations.

AUTHORS.

Leys, D.: Congenital Heart Block With Dextrocardia. Brit. Heart J. 5: 8, 1943.

A patient with congenital heart block, dextrocardia, and probable septal defect is reported. She also developed extensive pulmonary tuberculosis, but showed a good tendency to recovery, and attained the age of 23 years with good functional capacity equal to office work. Her ventricular rate was about 50, but rose to 80 during fever. It was not influenced by exercise or adrenalin.

AUTHOR.

Heilig, R.: The Pathological Heart Conditions in Hookworm Disease and Their Causes. Indian M. Gaz. 77: 257, 1942.

The observations on sixty-five cases of uncomplicated, afebrile, severe hookworm disease, reported and discussed above, make it certain that the pathologic heart signs

which are typical for this condition are due to a diffuse myocardial damage which leads to a considerable dilatation of the left and the right heart; the murmurs are not only hemic but also, most probably, consequences of a functional, supravulvular pulmonary stenosis and a relative mitral insufficiency, caused by the dilatation. In 90 per cent of these cases all the signs of myocardial degeneration and dilatation vanished quickly and almost completely in parallelism with the improvement of the erythrocyte count and hemoglobin level, in spite of the untreated and persisting hookworm infestation. Six cases showed no change of the pathologic heart condition before deworming, though the hemoglobin level rose from values of 10 to 15 per cent Sahli on admission, to 40 to 60 per cent before anthelmintic treatment was started; in these cases the heart dilatation and myocardial lesion improved quickly after complete destruction of the hookworms. These facts seem to prove that two factors are responsible for the heart damage in ancylostomiasis, the anemia and a toxic agent, dependent on the presence of the hookworm; in the majority of cases it is possible to compensate (temporarily?) the action of the second factor by curing the anemia, but a minority remains where this factor is predominant and exerts its myocardial damaging influence irrespective of the blood condition. No decision was reached as to whether this agent is a toxin or an allergin; the eosinophilia, said to be found frequently in ancylostomiasis, points toward the second possibility. Complete elimination of the hookworms, however, has to follow the antianemic treatment, preferably succeeded by prolonged iron medication, to get optimum and lasting results.

AUTHOR.

Evans, W.: Mitral Systolic Murmurs. *Brit. M. J.* 1: 8, 1943.

The need is discussed for an evaluation of these murmurs in the diagnosis of heart disease, and for examining the distinctive feature which may identify the murmur with some precise cardiologic disorder. The murmurs are divided into three categories: irrelevant, innocent, and mitral incompetence. The discussion is brief, but very inclusive, and gives proper emphasis to the relative importance of this physical sign.

MCCULLOCH.

Dassen, R., and Fongi, E. G.: Hamman's Syndrome. *Medicina, Buenos Aires* 3: 76, 1942.

A clinical case of Hamman's syndrome in a woman 23 years of age is described. The diagnosis is made and the basis to recognize it is given, showing its differences with pericarditis and acute coronary occlusion.

AUTHORS.

Moloney, W. C.: The Occurrence of Abnormal Capillary Fragility in the Newborn. *Am. J. M. Sc.* 205: 229, 1943.

In a preliminary study of capillary resistance in the newborn, thirty-three (60 per cent) of fifty-five infants showed more or less abnormal capillary fragility.

This decreased capillary resistance disappeared as the infants became older.

Various factors influencing permeability of the capillary wall are outlined, and the possible relationship of abnormal capillary resistance to hemorrhagic disorders in the newborn is postulated.

AUTHOR.

Coburn, A. F., and Moore, L. V.: Salicylate Prophylaxis in Rheumatic Fever, *J. Pediat.* 21: 180, 1942.

One hundred eighty-six young rheumatic subjects were observed before and following hemolytic streptococcal pharyngitis. Of forty-seven who received prophylactic doses of sodium salicylate, only one developed rheumatic fever. Of one hundred and thirty-nine untreated patients, fifty-seven developed rheumatic fever. These observations suggest that rheumatic fever can be prevented by the administration of salicylates during the respiratory infection and silent phase of the rheumatic infection. The mechanism appears to be the prevention of antigen-antibody precipitation.

KERSHBAUM.

Padilla, T.: Cardiovascular Syphilis in 1942. *Medicina, Buenos Aires* 3: 24, 1942.

The clinical aspects of syphilis of the heart and aorta are studied. Four forms of syphilitic aortitis are pointed out: first degree, simple aortitis or not complicated; second degree, aortitis with dilatation which can become aneurysm; third degree, aortitis with aortic insufficiency; fourth degree, aortitis with obstruction at the ostium of the coronaries.

The high value (100 per cent positive) of the biologic reactions should be noted (Wassermann and Kahn) for the diagnosis of aortic syphilis in nontreated patients, and the importance of precocious and intensive treatment to impede the development of serious syphilitic aortitis.

AUTHOR.

Smith, K. S.: Cardiac Syndromes Complicating Diabetes and Their Treatment. *Brit. Heart J.* 5: 1, 1943.

The evidence proving that diabetes conduces to early and severe arteriosclerosis, and, especially, coronary arterial disease and coronary thrombosis, has been reviewed.

The clinical features of forty-nine consecutive cases of diabetes associated with heart disease have been analyzed. The sexes were fairly evenly represented; the average age of the men was 62 years, and that of the women 61 years.

Hypertension was present in forty-four of the forty-nine patients (almost 90 per cent); in thirty-one instances the blood pressure was 180 mm. or more. As is usual in hypertension uncomplicated by diabetes the blood pressure frequently dropped swiftly and considerably on confining the patients to bed. Reasons were adduced for believing that hypertension in the diabetic was in some degree directly attributable to the metabolic fault.

A study was made of the manner in which angina of effort, spasmodic angina, coronary thrombosis, left ventricular failure, and congestive heart failure supervened in diabetics. Some case histories illustrating these events, and showing the relationship between the diabetic state and the cardiac development, have been summarized.

As a rule, patients with diabetes and some form of angina or heart failure were found to derive benefit from any necessary readjustments of regime or insulin dosage. Controlled observations were not, for obvious reasons, generally possible, but in a few patients, in whom this adjustment only was made, deterioration in the heart condition was replaced by improvement.

It has been concluded that, while the lives of patients with disease of the coronary artery are at serious risk, those of the "cardiac diabetics" are even more precarious. Coronary thrombosis in the diabetic is extremely hazardous.

Methods of treatment of cardiac complications in diabetes have been reviewed. The requirements of diet, fluid, insulin, glucose, and remedies directed to the heart

have been considered. The well-known principle that, in patients with heart disease, sudden reductions of blood sugar by diet or insulin are not well tolerated has been endorsed in the present study. In general, the use of insulin will be in such dosage as may be necessary to abolish acetoneuria and reduce severe hyperglycemia. To use insulin to procure stabilization or exact control of the diabetes in patients with additional heart disease is to court disaster.

AUTHOR.

Shrader, J. C., Young, J. M., and Page, I. H.: *Pyelograms in Patients With Essential and Malignant Hypertension*. *Am. J. M. Sc.* 205: 505, 1943.

The retrograde pyelograms of 100 hypertensives and 100 normotensives were studied to ascertain whether hypertension was associated with any constant pyelographic variation. Those which seemed more common in hypertensives were renal pelvises which were larger than average, and pelvises whose position was lower than average. Intrarenal pelvis, incomplete rotation (renal torsion), right-angled ureteropelvic juncture, and bifid pelvis were no more common than in normotensive patients. Hypertension was not associated with any significant variation in the size of the pelvis to the size of the calices, the general configuration of the pelvis, the pelvic axis, nor the number or morphology of minor calices.

The incidence of hypertension in patients who exhibited easily recognizable renal abnormalities as demonstrated by retrograde pyelograms was 22 per cent. The average mean arterial pressure of patients with abnormal pyelograms was the same as the average mean pressure of those with normal pyelograms. The incidence of significant renal abnormalities in an unselected group of hypertensives was 19 per cent.

The retrograde pyelograms of patients with essential hypertension do not differ significantly from those of normotensives. The incidence of urographic abnormalities in an unselected group of hypertensives appears to be no greater than in normotensives.

AUTHORS.

Daley, R. M., Ungerleider, H. E., and Gubner, R. S.: *Prognosis in Hypertension*. *J. A. M. A.* 121: 383, 1943.

Hypertension is important for two reasons: as an indication of an underlying disease, and because of the deleterious effects of the elevated blood pressure itself. The mortality from heart failure and degenerative atherosclerotic changes of the large vessels, such as the coronary arteries, which result from long-standing duration of hypertension without regard to its degree, is far greater than the mortality from such causes as malignant nephrosclerosis and apoplexy, which can be attributed more directly to a decided elevation of the blood pressure. It is evident, therefore, that an important consideration in prognosis is the proper evaluation of the duration of the hypertension, apart from its degree. Since the degenerative atherosclerotic changes may occur in the absence of advanced arteriolar disease, it appears that the grading of hypertension solely by arteriolar changes (blood pressure levels and reactivity, retinal examination, pectoral biopsy), which indicate the degree and not necessarily the duration of hypertension, has certain shortcomings. The extreme variability in the level of the blood pressure, diastolic as well as systolic, dictates reserve in drawing conclusions from casual blood pressure readings. The range of blood pressure in subjects with hypertension may be determined most simply by employing the breath-holding pressor test to determine the "ceiling," and over-breathing for a short period as a depressor test to determine the lowest level to which the blood pressure may be expected to fall.

Left ventricular hypertrophy and atherosclerotic changes, particularly in the coronary vessels and the aorta, are invariable accompaniments of elevated arterial pressure of long standing, and are serviceable as prognostic guides. Hypertrophy of the left ventricle can be determined by means of x-ray study and electrocardiography, which also serve to reveal arteriosclerotic changes in the aorta and coronary arteries. The electrocardiogram is somewhat more sensitive than roentgen findings for early detection of left ventricular hypertrophy, employing criteria established by study of a large number of normal and hypertensive subjects. There is a marked increase in mortality with progression in the electrocardiogram toward an abnormal pattern.

Other considerations, including heredity, sex, age, and the presence of associated conditions such as renal disease, diabetes, and obesity, are important in estimating the life expectancy and the benefit which may be expected from therapeutic procedures available at the present time. The advent of several new therapeutic approaches offers real promise that hypertension may be brought under some measure of control, and therefore prognosis becomes of great practical importance, both as a standard by which to evaluate new therapeutic procedures, and also as an indication in the proper selection of cases amenable to various forms of therapy.

AUTHORS.

Lewis, R. N., Werle, J. M., and Wiggers, C. J.: The Behavior of the Spleen in Hemorrhagic Hypotension and Shock. *Am. J. Physiol.* 138: 205, 1943.

In nine experiments on dogs, the changes in areas of exteriorized spleens were studied by the method of Barcroft and Stephens during hemorrhage, posthemorrhagic hypotension, and hemorrhagic shock following reinjection of the blood which had been withdrawn.

In confirmation of previous reports, it was found that the spleen contracts rapidly and extremely during hemorrhage, the area being reduced by 50 per cent or more. In extension, it was found that during a period of prolonged posthemorrhagic hypotension the dog's spleen undergoes a further slow contraction, does not increase on reinfusion of the withdrawn blood, but remains contracted whenever the duration and intensity of the hypotension are sufficient to create dynamic and pathologic signs of shock. Similar changes occurred in plasmapheresis experiments.

In the dog, splenic contraction does not contribute to elevation or maintenance of arterial pressure by virtue of the increased resistance induced in the splenic shunt, but by augmenting venous return and cardiac output. The spleen is not an organ which withdraws blood from active circulation in hemorrhagic shock. When the spleen is found large and congested at autopsy, other factors must have operated.

AUTHORS.

Warren, J. V., and Stead, E. A., Jr.: The Effect of the Accumulation of Blood in the Extremities on the Venous Pressure of Normal Subjects. *Am. J. M. Sc.* 205: 501, 1943.

Venous tourniquets at a pressure of 85 mm. Hg were applied to the upper thighs of six normal subjects.

The application of these tourniquets caused a decrease in venous pressure in both the external jugular and antecubital veins. The average fall in venous pressure in the external jugular vein was 53 mm. of water. The average fall in venous pressure in the antecubital vein was 23 mm. of water.

The decrease in venous pressure from the application of tourniquets to the upper thighs is greater in the external jugular than in the antecubital vein, because the arm veins tend to collapse when the venous pressure is lowered. After the vein walls are in contact, further lowering of the venous pressure proximal to the point of collapse produces no further decrease in venous pressure in the distal portion of the vein.

AUTHORS.

Homans, J.: *Vasomotor and Other Reactions to Injuries and Venous Thrombosis.* Am. J. M. Sc. 205: 313, 1943.

This is a classic discussion of the subject, expressing the author's own conception of the problem. It must be read to be appreciated, and the reading is well worth while.

McCulloch.

Schill, E.: *A Case of Spasm of the Vessels of the Respiratory Center With Secondary Lung Edema.* Cardiologia 6: 221, 1942.

A temporary spasm of the vessels supplying the breathing center, amenable to intravenously administered sodium nitrite, which well-nigh caused cessation of breathing, was accompanied with edema of the lungs in consequence of failing arterIALIZATION of the blood, and consequent poor nourishment of the heart muscles since the left half of the heart had been formerly damaged owing to hypertonia and previous thrombosis of the left coronary artery.

AUTHOR.

Cossio, P., and Fustinoni, O.: *Angina Pectoris and Diaphragmatic Hernia.* Rev. argent. de cardiol. 9: 217, 1942.

The literature upon the nature of the painful crisis in diaphragmatic hernia is reviewed, and five personal observations are reported in which these crises were erroneously considered as due to angina pectoris of coronary origin, or myocardial infarct.

The error in diagnosis was made because of the pain characteristics (intensity, localization, irradiation, effectivity of nitroglycerin) and the appearance of a coronary wave in the electrocardiogram, or because of an apparently irreducible cardiac insufficiency.

A few facts are pointed out which may avoid this diagnostic error. The electrocardiographic alterations are explained as due to inflammatory or mechanical action of the hernia upon the pericardial surface of the heart. The cardiac insufficiency is considered to be a consequence of vitamin B₁ deficiency, or of anemia which may follow circulatory or inflammatory alterations of the gastric mucosa.

It is maintained that the pain attacks are, at least sometimes or partly, of cardiac origin. It is appropriate, therefore, to speak of angina pectoris in diaphragmatic hernia, as well as in anemia, aortic stenosis, and aortic insufficiency.

AUTHORS.

Edwards, E. A., and Edwards, J. E.: *The Venous Valves in Thromboangiitis Obliterans.* Arch. Path. 35: 242, 1943.

Examination of the blood vessels of the lower extremities shows that thromboangiitis obliterans damages the venous valves extensively and seriously. The lesions

involving the valves are part of the changes in the blood vessels in general, first, inflammation; second, thrombosis; and third, dilatation secondary to the obstruction by the inflammation or thrombosis.

The valves may be disrupted by the inflammation. Their excursion may be limited by their involvement in the inflammatory exudate in the valve or in the vessel wall, or by the formation of adhesions.

In obstructive thrombosis the valve is destroyed by the organization and recanalization, any remaining portions being incorporated in the walls of the channel or channels. In mural thrombosis the cusps may be incorporated in the organizing tissue, or their excursion may be limited by thickening and adhesion.

The dilatation of the veins distal to areas of obstruction is associated with relative incompetence of the valve. The growth of reparative tissue often additionally thickens the cusps and makes them rigid. The thesis is presented that this may be but one part of a widespread proliferative change in thromboangiitis obliterans secondary to the obstruction of the blood vessels.

AUTHORS.

Edholm, O. G.: The Compensatory Mechanism of the Splanchnic Circulation During Changes of Posture. *J. Physiol.* 101: 1, 1942.

The mechanisms responsible for the fall in blood pressure in the feet-down position have been examined in the cat. Evisceration does not abolish the fall, but diminishes the vascular compensation. Removal of the liver, with or without evisceration, almost abolishes the fall of blood pressure in the feet-down position. The fall in blood pressure is due to the collection of blood in the liver, not in the splanchnic region although this area is partly responsible for the compensation following this fall. The recovery of blood pressure on restoring the animal to the horizontal position is due to the return to the right side of the heart of the blood which had accumulated in the liver.

KERSHBAUM.

Currens, J., and Barnes, A. R.: The Heart in Pulmonary Embolism. *Arch. Int. Med.* 71: 325, 1943.

A study of the heart was made in cases in which pulmonary embolism occurred. It is noted that the size of the heart in the surgical group of cases in which pulmonary embolism develops, and the surgical group in which pulmonary embolism does not develop, is essentially the same. Since chronic valvular defects and disease of the pericardium were excluded as causes of cardiac enlargement, this evidence indicates that hypertension does not predispose to pulmonary embolism among surgical patients. The heart was examined in thirty cases in which pulmonary embolism occurred, and evidence of acute infarction was found in five. In four of these cases, no significant obstruction was found in the coronary arteries, but in the fifth case there was fresh coronary thrombosis. One case in which there was prolonged shock is presented. In this case there was acute infarction involving the posterior wall of the left ventricle, without coronary thrombosis. The electrocardiographic differentiation of infarction of the posterior wall of the left ventricle, and pulmonary embolism, is illustrated and discussed, and the value of the chest leads in differentiating the two is stressed. The mechanism of the production of electrocardiographic changes is discussed, and a possible explanation for angina pectoris, which occasionally occurs in pulmonary embolism, is suggested.

AUTHORS.

Mayerson, H. S.: Roentgenkymographic Determination of Cardiac Output in Syncope Induced by Gravity. *Am. J. Physiol.* 138: 630, 1943.

Individuals who can stand quietly for at least twenty minutes show insignificant changes in the stroke and cardiac outputs during the standing period as determined by the roentgenkymographic method. Fainters show a marked decrease in these functions under the same conditions. If no marked movement occurs, the stroke output just before syncope is 25 to 35 per cent less than at the beginning of the standing period, while the cardiac output has diminished 21 to 43 per cent. The development of syncope in quiet standing is primarily due to the absence of adequate muscular contraction which results in a diminished venous return. The vasomotor failure is secondary.

AUTHOR.

Lowsley, O. S., and Cannon, E. M.: Aneurysm of the Renal Artery. *J. A. M. A.* 121: 1137, 1943.

Aneurysm of the renal artery is a rare clinical pathologic entity. Only seventy-five cases have been reported to date, including a case of true aneurysm diagnosed preoperatively and presented here.

A congenital defect in the wall of the renal artery, particularly at its bifurcation, is a hypothetic factor in the etiology of aneurysm. It is questionable whether trauma per se produces renal aneurysm.

Only twelve of the seventy-five reported cases were suspected prior to operation or death.

True aneurysm is usually asymptomatic. A few patients have complained of pain in the flank. The cardinal symptoms of false aneurysm are hematuria, pain, and tumefaction in the flank. The pathognomonic signs, pulsation and a systolic bruit, have been present in seven cases. The presence in the x-ray film of a ringlike shadow, with a dense periphery disrupted in one portion, and a rarefaction of the center in the kidney or hilar region, is suggestive of a renal aneurysm.

The treatment is surgical. In the literature, all patients presenting symptoms who were not operated on died. Of the twenty-nine patients subjected to nephrectomy, twenty-six survived. Of thirty-seven patients who underwent operation, eight died, an operative mortality of 21 per cent.

AUTHORS.

Darrow, D. C., and Miller, H. C.: The Production of Cardiac Lesions by Repeated Injections of Desoxycorticosterone Acetate. *J. Clin. Investigation* 21: 601, 1942.

Evidence is presented that cardiac lesions were produced by prolonged injections of desoxycorticosterone acetate in rats. The dose of DOCA was 1, 2, and 4 mg. daily, and the observations were made over a period of thirty to forty days. Necrosis of the myocardial fibers and replacement by fibroblasts were produced by these repeated injections. Pyridoxin intake did not influence the production of the lesions nor did a low intake of thiamin aggravate them. Diets low in potassium produced lesions in the heart which could not be distinguished from that produced by the repeated injections of DOCA. Only a suggestive lowering of the potassium in the cardiac muscle was found in contrast to a more definite lowering of the potassium in the skeletal muscle.

The cardiac lesions produced by injections of DOCA or diets low in potassium can be prevented by addition of potassium chloride to the drinking water. Deficit of body potassium is apparently essential for the production of these lesions.

GRACE M. ROTH.

Lebowich, R. J.: Chemotherapy of Experimental Streptococcic Pericarditis: A Comparison of Sulfanilamide and an Acetylated Derivative of 4,4'-Diaminodiphenylsulfone Hydrochloride in the Treatment of Experimental Beta Hemolytic Streptococcus Pericarditis in the Rabbit. *Arch. Path.* 35: 253, 1943.

It has been shown for the strain of beta hemolytic streptococcus investigated that an acetylated derivative of 4,4'-diaminodiphenylsulfone hydrochloride exercises a distinctly beneficial effect on the natural course of experimental beta hemolytic streptococcus pericarditis in rabbits. It considerably increases the number of cured survivors in comparison with their complete absence in the sulfanilamide-treated group, and definitely prolongs the average duration of life beyond that of the control and that of the sulfanilamide-treated group. The most effective results were obtained in a group of fifty rabbits whose treatment was initiated twelve hours after the production of pericarditis; forty-nine of these animals were cured. The incidence of survivors and the prolongation of life are definitely related to the time of starting treatment.

The toxicity of this compound is of a relatively low order.

The results are on a scale sufficiently large to indicate that the acetylated derivative of 4,4'-diaminodiphenylsulfone hydrochloride is far superior to sulfanilamide in its therapeutic effect on beta hemolytic streptococcus infection of the pericardium as observed in rabbits.

AUTHOR.

Gefter, W. I., and Leaman, W. G., Jr.: The Use of Ouabain in Rapid Cardiac Arrhythmias. *Am. J. M. Sc.* 205: 190, 1943.

One intravenous dose of ouabain produces a statistically significant reduction in ventricular rate and is an effective method of treating rapid cardiac arrhythmias of auricular origin. It is relatively ineffective when the mechanism is that of a simple tachycardia or when complicated by severe infection.

When combined with one oral dose of digitalis, intravenous ouabain is an effective aid in producing full digitalization.

AUTHORS.

Goldsmith, G. A., and Cordill, S.: The Vasodilating Effects of Nicotinic Acid (Relation to Metabolic Rate and Body Temperature). *Am. J. M. Sc.* 205: 204, 1943.

The administration of nicotinic acid produced no significant change in metabolic rate or body temperature before the appearance of the characteristic skin reaction. The vasodilatation, therefore, does not seem to be compensatory to increased heat production. Available evidence at the present time suggests that the vasodilator response is due to a local effect on the arterioles in the skin.

AUTHORS.

Book Reviews

THE EPIDEMIOLOGY OF RHEUMATIC FEVER AND SOME OF ITS PUBLIC HEALTH ASPECTS:

By John R. Paul, M.D., Professor of Preventive Medicine, Yale University School of Medicine, and other contributors; second edition, 1943. Printed by the Metropolitan Life Insurance Company for the American Heart Association. 163 pages, 31 illustrations.

Of the various chronic infectious diseases of the United States, rheumatic fever now ranks behind only tuberculosis and syphilis as a cause of illness and death. Judging from the trend in recent mortality and morbidity statistics, one can venture the prediction that within another half century rheumatic fever will occupy first place in this group of diseases. For this reason and also because of the importance of the disease in military medicine, a review of the factors which control its incidence and spread is particularly timely at present. Dr. John Paul's book meets this need in a thoroughly admirable fashion. In the brief space of 150 pages he has covered a great amount of material, and has summarized all of the important studies of the past two decades. These recent studies have been well integrated with the historical aspects of the disease.

The tone of the book is judicial throughout. Both sides of controversial questions are considered in a critical but thoroughly unprejudiced manner. The recent work bearing on the relationship of hemolytic streptococcal infections to the disease is reviewed, and the author concludes that although there is rather overwhelming evidence to indicate some relationship, such evidence does not yet permit one to draw the conclusion that the hemolytic streptococcus is the only noxious agent concerned.

A large portion of the book is devoted to a discussion of various host factors, including age, sex, and racial predisposing factors, as well as the influence of living conditions and climate. There is also a comprehensive discussion of rheumatic families; the author cites the evidence which indicates that contagion alone cannot account for the prevalence of the disease in such families, and, therefore, states that hereditary susceptibility must be assumed.

The last two chapters deal with possible future Public Health procedures, by D. D. Rutstein, of the Cardiac Bureau, New York State Department of Health, and with general principles concerning the care of chronic rheumatic fever and rheumatic heart disease, by T. Duckett Jones of the Good Samaritan Hospital in Boston. These chapters are, likewise, thoroughly modern, and critically written.

The style of the book is unusually readable, and the material is presented in such a clear fashion that it can be readily assimilated by a second-year medical student, or even by a layman who has the barest acquaintanceship with medicine. This is not to be taken to mean that the book is written primarily for such persons. There is a wealth of material which can be profitably read by general practitioners, internists, and Public Health physicians.

Dr. Paul's book is not for sale; it was published for the American Heart Association, and the Metropolitan Life Insurance Co. has generously borne the cost of publication. Physicians whose special interests and activities entitle them to the book may obtain it free of charge by writing to the American Heart Association. Copies have already been sent to hospitals, camps, libraries, and certain individual officers in the United States Army.

TINSLEY R. HARRISON.

PHYSIOLOGY IN AVIATION: By Chalmers L. Gemmill, M.D., Commander, M.C., U.S.N.R., Associate Professor of Physiology, Johns Hopkins University School of Medicine, Instructor in Physiology, School of Medicine, Naval Air Station, Pensacola, Fla. Charles C Thomas, Springfield, Ill., 1943, 124 pages, 18 figures, 18 tables, \$2.00.

The author has been in charge of the course of lectures on aviation physiology at the School of Aviation Medicine of the Naval Air Station at Pensacola, Fla. This little book contains the material covered in the lectures, and offers a clear and simple summary of the basic physiology necessary for an understanding of the reactions of men exposed to the hazards of altitude.

The book is intended for beginners in the subject and seems well adapted to the purpose. Advanced students will regret the lack of a bibliography, and some may question whether subject matter such as this should be presented, even to beginners, with so little hint of the difficulties and doubts involved.

ISAAC STARR.

ANOXEMIA CARDIACA, EXPERIMENTAL Y CLINICA: By Dr. Moises Sloer, Profesor Adjunto de Patologia, Rosario. Tesis de Profesorado, Rosario, Argentina, 1942, 69 pages.

The author reviews the chief studies on cardiac anoxemia, from Rothschild and Kissin, to Levy and co-workers. Experimental and clinical observations follow. Experiments on dogs with different gas mixtures show that *anoxemia* causes increase of respiratory rate, hypertension, and tachycardia. These changes are reversed by breathing mixtures containing less than 3 to 4 per cent of oxygen. These mixtures also cause many electrocardiographic changes, such as nodal rhythm, A-V block, inversion of T, and deviation of S-T from the base line.

Clinical observations were made on thirty cases, including normal subjects, doubtful cases, and heart patients. *Anoxemia* caused increased frequency of respiration and lowering of the T wave of the electrocardiogram in the first two groups; everything else remained practically unchanged. The height of the T wave decreased more in doubtful heart cases than in normal persons. The administration of pure oxygen after anoxemia brings back normal conditions. Anoxemia causes the following electrocardiographic changes in heart patients: tachycardia; no changes of either P or P-R; decrease of R; flattening or inversion of T; and displacement of S-T from the base line. In general, the changes were greater in this group than in the two others. The author finds in these changes a confirmation of the anoxemic theory of angina pectoris. He does not believe, however, that electrocardiographic changes can be used as a test of coronary insufficiency.

Therapeutic use of oxygen is recommended in all heart cases when coronary insufficiency is present.

A. LUISADA.

EL PULSO VENOSO NORMAL: By Agustín Caeiro, Córdoba, Argentina. S. de Amorrortu, Buenos Aires, 1942, 148 pages, 57 illustrations.

This booklet reviews in a clear and complete way the studies on jugular vein tracings from Wedemeyer to Orfás. After discussing the factors which regulate the venous circulation, the mechanism of production of the different waves is described. In one of the most interesting chapters the author reports his own studies on the velocity of the waves in the venae cavae of dogs. From the clinical and experimental observations on venous tracings, the author concludes that each wave of the venous pulse is the result of the combined action of changes in the volume of the

vein, changes in the pressure, and changes in the velocity of the venous blood flow. In another chapter there is an accurate description of the time relations between the waves of the jugular tracing and those of other tracings. This will be of use to students of the circulatory apparatus. At the end of the book there is an extensive summary in both Spanish and English.

ALDO LUISADA.

Errata

In the article entitled "The Effect of the Intravenous Administration of Lanatoside C Upon the Output, Diastolic Volume, and Mechanical Efficiency of the Failing Human Heart," by John S. LaDue and George Fahr, which appeared in the March, 1943, issue of the *JOURNAL*, volume 25, page 344, the following corrections should be made: In Fig. 2 the value for V_D should be 885.3 cm.³, and, for V_S , 844.4 cm.³; in Fig. 3, V_D should be 738.7 cm.³, and V_S , 691.4 cm.³

In the paper by Dr. Henry I. Russek, entitled "Blood Pressure in the Aged," which appeared in the July, 1943, issue of the *JOURNAL*, volume 26, page 11, the sentence under Table IV, which reads "Percentage variation from unexpected mortality" should be "Percentage variation from expected mortality."

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Original Communications

THE ABSENCE OF CONSPICUOUS INCREMENTS OF VENOUS PRESSURE AFTER SEVERE DAMAGE TO THE RIGHT VENTRICLE OF THE DOG, WITH A DISCUSSION OF THE RELATION BETWEEN CLINICAL CONGESTIVE FAILURE AND HEART DISEASE

ISAAC STARR, M.D., WILLIAM A. JEFFERS, M.D., AND
RICHARD H. MEADE, JR., M.D.
PHILADELPHIA, PA.

PERIPHERAL venous congestion is often interpreted by clinicians as indicating disproportionate failure of the right ventricle.^{1, 2} Doubt of the validity of this interpretation^{3, 4} stimulated us to attempt direct experiments on dogs. The controversy between those who believe that one side of the heart can fail while the other remains relatively competent and those who can conceive only of failure of the whole heart has been recently reviewed by Luisada.⁵ In the experimental attack on this problem, interest has centered in the production of pulmonary edema by damaging the left side of the heart.⁵ Therefore, although the right side of the heart has been damaged by ligation of the right coronary artery⁶ or the injection of silver nitrate into the right ventricular wall,^{7, 8, 9} these experiments were designed as controls, and the facts which chiefly interested us were not recorded.

Therefore, in acute experiments, we damaged the exposed right ventricular wall with a cautery, and, in chronic experiments, ligated the vessels supplying this wall, closed the incision, and studied the animals until death or recovery ensued. Only minimal changes of venous pressure followed the most extensive damage to the right side of the heart that we knew how to inflict. With the results of these experiments before us, we have reconsidered the dynamics of clinical congestive failure and discussed its relationship to weakness of the heart.

From the Hartzell Research Department of Therapeutics, the Robinette Foundation, and the Harrison Department of Surgical Research of the University of Pennsylvania.

The completion of this work was assisted by a grant from the Daland fund of the American Philosophical Society.

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ACUTE EXPERIMENTS

Dogs were anesthetized with 1 c.c. per kilogram of a solution containing 3 per cent morphine, 4.2 per cent chloralose, and 50 per cent urethane, injected intraperitoneally, and were given ether during the operation, if necessary. Carotid and femoral venous cannulae were inserted; the former was connected to a mercury manometer, and the latter to a manometer and a reservoir of physiologic salt solution. Venous pressures were taken by filling the manometer a little above the venous pressure and allowing the saline to run into the vein until equilibrium was secured.

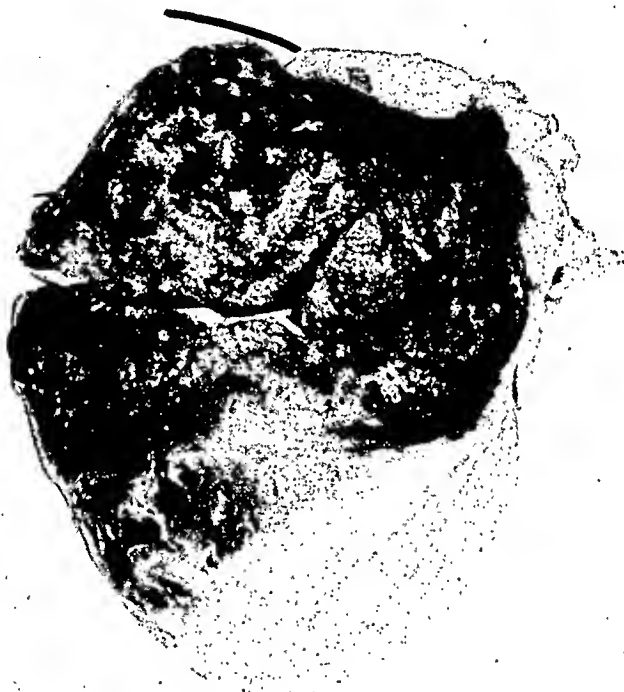


Fig. 1.—The heart of Dog 41 after the right ventricular wall had been attacked repeatedly with a cautery. The lesion had been cut through, to permit estimation of its depth, when this photograph was taken.

Under artificial respiration the sternum was split and the pericardium divided to expose the heart. After a control period, a red-hot soldering iron was laid repeatedly all over the surface of the right ventricle to destroy the muscular layers and interrupt the superficial blood vessels. Observations of arterial and venous pressure were taken while reheating the cautery, so that these estimations alternated with the infliction of more damage. Soon the right ventricle ballooned out at each systole. When rupture threatened, usually when leakage actually began, the experiment was terminated by stopping the respiration pump. After death the heart was removed, and the right coronary artery cannulated at its mouth and injected with hot, colored gelatin. After

examination and description of the heart, pieces were taken for sectioning, and the rest preserved in formalin.

The results are recorded in Table I; the venous pressure was measured from an imaginary horizontal line halfway between the anterior and posterior aspects of the chest. The most extensive damage to the right ventricle was followed by an increase in venous pressure of a little less than 2 cm. H_2O in one experiment, about 1 cm. in two experiments, and by no significant change in the other. However, after the pump was stopped, the asphyxial response caused a high rise of venous pressure in each animal.

Post-mortem examination showed that the largest part of the right ventricular wall was destroyed completely and most of the remainder could not be injected, presumably because the supplying vessels had been interrupted, but small areas of the right ventricular surface usually escaped the cautery. The post-mortem findings in Dog 41 were fairly typical of all, and this heart is shown in Fig. 1. Gross examination showed that over two-thirds of the right ventricular pericardial surface was charred. Viewed from within, the endocardium under this area showed gray areas and hemorrhagic spots. Cuts through the lesion showed that the tissue which retained its normal color was less than 2 mm. thick in many places. A strip of right ventricle wall on the right margin, about one-fifth of the total ventricular surface, was not reached by the cautery. This area appeared normal, and blood vessels here were injected, but no other injected vessels were found in any part of the right ventricular wall. The left ventricle was normal. Examination of microscopic sections confirmed the gross impression. At least three-fourths of the right ventricular wall must have been functionless at the end of the experiment.

Evidently, therefore, destruction of a large part of the right ventricular wall was followed by little or no increase in venous pressure in our experiments; certainly nothing comparable to that seen in human heart failure was observed. However, the direct transference of our results to heart failure in man would be open to criticism. Since, with the chest open, venous pressure and venous return are not under their normal influences, our dogs might have failed to show a more conspicuous elevation of venous pressure because they were unable to do so, i.e., because the mechanisms needed had been destroyed by the anesthetic or the operative procedure. This very proper objection can be answered in part. When the animals were asphyxiated by stopping the pump, the venous pressure reached 14 to 18 cm. H_2O —levels equal to, or only slightly below, those found in many cases of human heart failure. Therefore, our dogs did not fail to increase venous pressure merely because the open chest or the operative procedure made a larger increase impossible. Nevertheless, the mechanism might be different in the two situations, so we sought further assurance in chronic experiments on unanesthetized animals with the chest closed.

TABLE I

ACUTE DAMAGE TO THE RIGHT VENTRICLE OF ANESTHETIZED DOGS, WITH CHEST OPEN AND ARTIFICIAL RESPIRATION

TIME	MEAN B. P. (MM. HG)	VENOUS PRES- SURE (CM. H ₂ O)	EXP. DOG 40 7.2 KG.	TIME	MEAN B. P. (MM. HG)	VENOUS PRES- SURE (CM. H ₂ O)	EXP. DOG 41 13 KG.
3.34	110	6.3		2.36	114	8.0	
3.45	120	6.5		2.37	114	8.5	
3.52	126	6.3		2.41	114	7.9	
3.58	132	6.5		2.42	114	8.3	
4.07	126	5.9		2.46	124	7.9	
4.10			Damage to R. V. begun	2.49	126	7.6	
				2.53	130	7.8	
				2.54			Damage to R. V. begun
4.11	134	6.0		2.56	120	7.8	
4.15	116	5.7		3.00	120	7.8	
4.20	104	5.9		3.10	118	7.4	
4.24	90	6.1		3.24	130	8.0	
4.31	90	5.8		3.29	124	8.3	
4.36	86	5.8		3.34	124	9.0	
4.45	74	6.7		3.37	120	9.0	
4.51	64	6.4		3.50	120	8.3	R. V. per- forated
4.58	66	7.1					Art. resp. off
5.06	70	7.9					
5.12	74	8.3		3.55		14.0	
5.16	70	8.1					
5.22		18.0	Art. resp. off				
EXP. DOG 42 9.3 KG.				EXP. DOG 44 9.5 KG.			
				2.55	130	7.8	
				3.01	134	7.8	
3.02	68	6.6		3.04	134	8.0	
3.11	76	6.8		3.07	136	8.0	
3.12			Damage to R. V. begun	3.08			Damage to R. V. begun
				3.11	128	8.6	
3.14	74	6.8		3.15	112	8.7	
3.19	84	6.3		3.19	94	8.6	
3.28	90	6.5		3.27	76	8.3	
3.39	88	6.2		3.28	170	16.0	Art. resp. off
3.46	90	6.5					
3.54	92	6.5					
3.58	92	6.5					
3.59	148	15.0	Art. resp. off				

CHRONIC EXPERIMENTS

Hill, Johnston, and Wilson,⁶ reporting late electrocardiographic effects after ligation of the right coronary artery, had demonstrated that dogs could survive this damage to the right side of the heart for long periods. These authors were interested in the electrocardiographic changes, and venous pressure was not measured. Communication with Dr. Wilson disclosed that no venous congestion had been observed; and we had no doubt that, if conspicuous venous congestion had occurred, it would have been both noted and reported. Nevertheless, it seemed wise to repeat this type of experiment, and make careful measurements of venous pressure.

After appropriate anesthesia, and with a sterile technique, the visible branches of the right coronary artery, descending on the surface of the right ventricle, were ligated, and the animals allowed to recover. Several dogs did not survive the operation; one lived thirty-six hours, and one recovered completely and was sacrificed after three months. In the two survivors, venous pressure was estimated by training the dog to lie quietly on its back and measuring the height of the column of blood distending the large superficial vein on the interior aspect of the hind leg. When the skin was shaved, this could easily be seen, and the vein could be filled and emptied by raising or lowering the limb, much as the veins on the back of the hand are studied in man.

TABLE II
VENOUS AND ARTERIAL PRESSURES IN DOGS WITH INFARCTS OF THE RIGHT VENTRICULAR WALL

DATE	VENOUS PRESSURE (CM. H ₂ O)	REMARKS
3/24		Dog 378. Operation, all visible branches of the right coronary artery ligated
3/25	4.0	Dog weak
3/26		Dog found dead, necropsy lost by accident
2/20		Dog 539. 7.8 kg. Operation, several branches of right coronary ligated
2/27	5.5	Dog weak
3/6	4.0	Dog appears well and lively
3/13	3.0	Dog appears well and lively
3/20	5?	Dog has distemper but is lively
3/30	6.5	Dog has distemper but is lively
4/15	4.0	Slight nasal discharge persists
4/24	4.0	Appears well and lively
5/12	7.5	Appears well and lively
5/26	4.0	Appears well and lively
5/27		Dog sacrificed

The results are recorded in Table II. No substantial increases in venous pressure were found. Palpation for the liver and auscultation of the chest revealed nothing abnormal at any time.

We followed one dog for three months and then sacrificed it. A large infarct, roughly 3 by 4 cm., could be clearly identified in the surface of the right ventricle. No other cardiac lesions were found.*

DISCUSSION

It is well known that the right coronary artery may send branches to the left ventricle, and it is therefore entirely possible that, in tying or cauterizing vessels on the right ventricular surface, the blood supply to a portion of the left ventricle was interrupted. However, no lesion of the left ventricle was demonstrated at necropsy in any experiment. Also, if the right ventricle is weakened, and its output diminishes, the left side of the heart will not be as well filled, to the detriment of its function, even though its potential strength may be intact. But although we are prepared to admit that left ventricular function may

*Dr. W. E. Ehrlich of the Pathology Department assisted in the necropsy.

have been impaired by our procedures, the total destruction of such a large part of the right ventricular wall, and its lack of function as judged by systolic bulging during life and our inability to inject the vessels after death, make it obvious that the right ventricle was disproportionately weak in relation to the left. Manifest systemic venous congestion and increased venous pressure have often been attributed to such a disproportion of cardiac strength, but in our hands the direct experiment failed to reproduce these effects.

In view of the negative character of our results and the absence of any mention of congestion in other experiments⁶⁻⁹ in which the right ventricle was damaged, one wonders how the conception that venous congestion indicates right-sided heart failure originated. When asked this question, many intelligent clinicians of our acquaintance have supported their views by the dam and stream analogy, as have some leaders in this field.¹⁰ They conceive of a stream with a dam, forming a mill pond, and of the heart as a pump to lift water over the dam. If such a pump weakened, obviously the water in the mill pond would rise.

This analogy is popular because, since it is within the experience of everyone, the facts are very easily grasped. But the difficulty should be apparent as soon as it is pointed out; in the example cited there is no circulation. To make this analogy closer, although it would still be very imperfect, one might conceive of the pump drawing water from the pond, but also pumping this water back into the pond again, its only source of supply. One easily sees that under these circumstances the rate of pumping has no relation to the level of water in the pond.

But two other arguments cannot be dismissed so lightly. In our circulation schema,³ when the left "heart" was weakened, "blood" was transferred from the systemic to the pulmonary circuit, and, when the right "heart" weakened, from the pulmonary to the systemic. One would certainly expect similar mechanical effects to take place in the body when one side of the heart weakened. But while it is easy to think of blood drawn from the systemic circuit flooding the lungs in left-sided heart failure, one wonders whether blood spared from the lungs could possibly produce the massive venous and hepatic congestion we so often see in the clinic. Indeed, more blood than the normal lungs are believed to contain has often been transfused into the systemic veins without reproducing a noteworthy degree of venous congestion. Therefore, although we concede that right-sided heart failure may be a factor in clinical systemic venous congestion, the evidence indicates that it plays only a minor part. It is to be noted that the venous pressure did rise a little in some of our acute experiments, especially in Dog 40, in which the arterial blood pressure was maintained. Transference of blood from the lungs was doubtless a factor in this effect.

Another mechanical effect which increases the amount of "blood" in the "veins" can be easily demonstrated in any circulation schema with a pump, valves, elastic tubes, and a peripheral resistance. In such

a system, as "cardiac output" diminishes, "arterial" pressure falls and "venous" pressure rises as "blood" is transferred from the "arterial" to the "venous" side. In our animals this process may well have been a factor in the small increments of venous pressure which, late in the experiments, accompanied a diminishing arterial blood pressure. But physiologists who are inclined to give great weight to this analogy do not, perhaps, realize that manifest venous congestion is not regularly found in moribund states, although the arterial pressure falls and the circulation must always diminish before it comes to rest. Therefore, one must conclude either that this mechanism is not of sufficient importance to produce manifest congestion of veins of patients, or that its effect is regularly overcome by another mechanism, such as a general relaxation of peripheral vessel tone, which must be assumed to occur as death approaches, and to be absent in congestive heart failure. Regarded in either way, it is evident that this mechanical effect of a diminished circulation is of less importance than other mechanisms which may influence venous pressure.

But if the massive venous congestion which we so often see in the clinic is not due to predominantly right-sided heart failure or to diminished cardiac output,^{1, 11} to what should it be attributed? Clinicians have been slow to realize the multiplicity of noncardiac factors which might cause venous congestion and increased venous pressure. On the other hand, physiologists have suffered from the lack of a clear conception of certain facts about congestive failure as we see it in the clinic. Three such facts which bear on any theory of congestive failure may now be reviewed.

First, the venous congestion of cardiac patients persists in large measure after the heart has ceased to beat.⁴ After death, the average pressure in the veins of cardiac patients who died with venous congestion exceeds that of patients who died without heart disease by an amount approximately equal to the difference present during the last illnesses. This fact surely indicates that any connection between venous congestion and cardiac function must be indirect, for the abnormality persists after cardiac function has ceased.

Second, bimanual pressure with one hand above, and one below, the right upper quadrant will distend the neck veins of many patients with heart disease; this maneuver has been used as a test for incipient congestive failure in Europe. In such patients the difference between the congestion during this pressure and its disappearance when pressure is released is surely not due to any change in the potential strength of the heart. It is obvious, therefore, that changes in the peripheral circulation are able to determine the presence or absence of venous congestion in these cases.

Third, the diuresis caused by mercurial diuretics often leads to rapid disappearance of the venous congestion. The disappearance of venous congestion which follows the administration of digitalis or the xanthines

may be attributed to improvement of the circulation from cardiac stimulation, but, when a similar effect follows the administration of a mercurial diuretic, this explanation is not valid, for mercury depresses the heart in any concentration that affects it at all.¹² Apparently, the common factor in the action of these three groups of drugs is their ability to eliminate fluid from the body; and the benefit which often follows a low salt diet¹³ or the direct removal of fluid by tapping or Southey's tubes is additional evidence of the importance of this factor. Here we have evidence of another factor in the genesis of venous congestion which is only remotely, if at all, related to the heart.

With these facts in mind, let us attempt to assay the more important factors which might contribute to venous congestion in man. The first to consider is distention of the elastic vessels by the increased volume of blood which is so regularly found to accompany congestion of the veins in tests made during life.¹⁴ Passive distention due to hypervolemia is a satisfactory explanation for the increased pressure throughout the vascular system, i.e., the increased static pressure which is found after death in cases in which there was venous congestion during life.⁴ But unless the methods are playing us false, not all patients with hypervolemia, e.g., in polycythemia vera,¹⁵ have venous and hepatic congestion. Therefore, the blood vessels must be assumed to play an active part in both the pressure and the distribution of blood within them.

That a widespread increase of vascular tone can raise venous pressure was first suggested to us by results in an animal experiment reported before,¹⁶ in which, during the early part of the asphyxial response, cardiac output and arterial and venous pressure were increased at the same time. The asphyxial rise in venous pressure in the experiments reported in Table I of this paper was doubtless of this type, for the heart was observed to be beating with increased vigor when arterial and venous pressures were elevated. Such a generalized increase in intravascular pressure cannot be explained as the mechanical consequence of changes in cardiac activity and arteriolar resistance. Occurring far too rapidly to allow the assumption of an increase in blood volume with passive distention of vessels, a widespread increase in vascular tone, without compensatory relaxation elsewhere, is the explanation which naturally suggests itself. That a similar widespread increase in vascular tone might take place in man has been suggested.¹⁷

Pressure on blood vessels from without, as by fluid in the body cavities or when edema distends the skin, must be another factor, for this would produce much the same effect as active contraction of vessel walls. But since large hydrothoraces, ascites, and the massive edema of nephrosis are often unaccompanied by venous congestion, this factor is probably a small one in most cases.

Nevertheless, a qualification must be made concerning the factors which we believe to be minor. In normal subjects many veins are partly collapsed, and the circulation obviously has an easily available

reserve capacity. It is under such conditions that transference of blood to the veins by the factors we have called minor causes little manifest congestion and little or no pressure changes; but if the vascular system were full and the veins already distended, the transference of small amounts of blood to the veins would have a much greater effect on the pressure within. Thus, it is only when it acts by itself that we expect cardiac weakness to cause no manifest venous congestion; surely, our hospitals are full of cases of angina pectoris without venous congestion. But if the blood volume was first increased, one would expect the minor factors to be more potent, so that the hearts' strength might be more accurately reflected by changes in venous pressure.

The direct experiments on dogs, the behavior of our circulation schema,³ and the studies made on man⁴ provide evidence against the commonly accepted doctrine of a direct mechanical relation between the heart and what is called congestive heart failure, but this evidence does not deny a relationship of another kind. The evidence for some kind of relationship is strong indeed; it consists of the impressive frequency of this complication late in the course of patients who have been long afflicted with chronic heart disease of many types. Other evidence, obtained in this laboratory,¹⁸ supports this conception, for, using a physiologic measure of cardiac strength, namely, the ratio of the left ventricle's work per beat to the size of the heart, cardiac weakness was found to be characteristic of those patients who had passed through congestive failure, and so could be expected to suffer from it again. But in these data, also, there is evidence against a direct mechanical relationship, for no congestion was present when these tests were made, even though cardiac weakness was demonstrated. Nevertheless, it must be emphasized that this evidence and our failure to produce manifest congestion by directly damaging the heart does not refute the possibility of an indirect relationship, with time-consuming physiologic steps in between.

A plausible train of events relating the heart and venous congestion is suggested by McMichael's data:¹⁹ The heart weakens and the circulation diminishes; as the bone marrow is stimulated by oxygen lack, the blood volume increases; the excess blood accumulates in the veins and congests them; and better cardiac filling from the increased venous pressure improves the cardiac output, so that normal circulation may be regained in some cases.

In the present state of our knowledge, other trains of events can also be conceived: The weakening heart could be thought of as diminishing renal circulation, for there is certainly good evidence of diminished kidney function in cardiac cases; specific renal insufficiency might cause the characteristic retention of fluid and electrolytes; this retained fluid increases blood volume and accumulates in tissues pressing on the patent vessels; to accommodate the excess, blood accumulates in the most distensible vessels, the veins, and also in the lungs, where it displaces some

of the air, and symptoms such as dyspnea result. Whether such fluid retention could explain the whole picture is debatable, but the prompt relief obtained by many patients when diuresis is established is most suggestive.

The similarity of the manifestations of overdosage with desoxycorticosterone²⁰ to those of congestive failure permits one to speculate about a train of events going through the endocrine system, and this does not exhaust the possibilities.

None of these speculations result in a perfectly satisfactory theory, for neither do the signs and symptoms of congestive failure regularly follow prolonged exposure to anoxemia at high altitudes, nor do all renal lesions which cause retention of water and electrolytes cause venous congestion. Knowledge about the action of desoxycorticosterone is still too scanty to permit an opinion of the closeness of the analogy. Indeed, although the old conceptions no longer satisfy us, we have nothing equally definite with which to replace them.

But one point must be strongly emphasized. As soon as one abandons the conception of a direct mechanical relationship between heart disease and congestive failure, and tries to substitute a train of events, one must concede that there may be other causes of congestive failure than heart disease. For example, if anoxemia of the bone marrow is a link in the chain, anoxemia from causes other than heart disease should cause congestive failure. If the chain goes by way of the kidney, renal lesions might cause it. It is sobering to reflect that, in many cases of congestive failure, heart disease was not the initial event; renal disease, as in the hypertensive cases, or pulmonary disease is often the initial event in the train. We have records of cases of this type in which the heart muscle at necropsy showed little or nothing to suggest that it was weak. One can contend that the pathologists' methods are inadequate, but it is becoming apparent that other explanations are possible.

The pathologist is unable to tell from post-mortem examination of the heart which patients have died in congestive failure. A heart muscle which appears grossly and microscopically normal at necropsy is often judged by clinicians to have been weak during life. It is our contention that the criterion for cardiac weakness that is usually employed, namely, the presence of venous congestion, is unsatisfactory. It is to be hoped that, as knowledge improves, the clinical and pathologic evidence of cardiac weakness will be brought closer together.

Knowledge of the dynamics of venous congestion in man is still far from complete; the point to be made here is that factors concerned with the volume of blood and the tone of the blood vessels seem most likely to be able to cause it, and that the mechanical factors directly connected with weakness of the right side of the heart, or of the whole heart, seem less important. This conclusion is supported by the results of our experiments.

CONCLUSION

By directly damaging the right ventricle of the dog's heart in acute and chronic experiments we failed to produce more than a minimal increase in peripheral venous pressure. Our results give no support to the view that the peripheral venous congestion and the large increment of venous pressure so often associated with cardiac disease in man are caused directly and predominantly by failure of the right ventricle.

The relation of cardiac disease to venous congestion in man is discussed.

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THE TETRALOGY OF FALLOT

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WE HAVE had the opportunity of studying, at necropsy, the organs of two patients, 53 and 43 years old, respectively, whose hearts showed the complex of lesions commonly described as the tetralogy of Fallot. These include pulmonie stenosis, defect of the interventricular septum, dextroposition of the aorta, and hypertrophy of the right ventricle. These cases are unusual in a number of respects, not the least of which was the long period of survival. Abbott¹ considered twenty-five years to be the maximum duration of life, although she listed certain cases in which the patient lived longer. As far as we have been able to ascertain, only one case has been reported in which the patient survived longer than the first of our two patients, namely, Paul White's noted musician.³ It is apparent that the functional disturbances caused by the tetralogy are of a very serious nature, and are not consistent with life for more than a relatively short time. It is of great interest that in both of our cases there were factors which, although different in each, tended to alleviate the serious functional changes. These mitigating factors may explain, in part, the unusual longeivity of both our patients.

REPORT OF CASES

CASE 1.—This patient was 53 years old at the time of his death. He was born in Czechoslovakia, and had lived in the United States for 35 years. He worked as a coal miner for many years, and as a laborer and building superintendent. No information is available concerning details associated with his birth. He recalled, however, having been warned during childhood "not to run too much" because he had a "bad heart." The patient stated that he had "always" experienced dyspnea on severe exertion, which had impeded, but did not prevent, arduous physical labor.

At the age of 37 years, sixteen years before death, the patient noted the onset of frequent attacks of fleeting migratory joint pains involving nearly all the joints of the body, and occasionally accompanied by fever. Eighteen months before death the patient was confined to bed for about two weeks because of dyspnea, orthopnea, and edema of the ankles. These symptoms disappeared with rest in bed alone. Eleven months before death the patient was admitted to another hospital because of dyspnea at rest, orthopnea, edema of the face and ankles, cough, bloodtinged sputum and frequency of urination. On admission there, his temperature was 98.6° F., his pulse rate, 76, his respiratory rate, 20, and his blood pressure, 140/70. The patient was "somewhat" cyanotic and the neck veins were dilated. A moderate number of medium moist râles were present at the bases of the lungs, together with some scattered dry râles. The point of maximal impulse of the heart was at the mid-clavicular line. There was an increase in dullness to the right of the sternum.

From the Department of Pathology, Welfare Hospital for Chronic Diseases, New York City. Case 1 is from the First Medical Division, Dr. Walter Lough, Director. Case 2 is from the Third Medical Division, Dr. J. Murray Steele, Director.

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Systolic and diastolic apical thrills were noted, and systolic and diastolic murmurs were present over the entire precordium; their maximal intensity was in the fifth intercostal space to the left of the sternum. The murmurs were thought by another observer to be loudest at the apex and transmitted to the left axilla. The edge of the liver was felt 2 cm. below the costal margin. The extremities showed "early clubbing" and "1 plus cyanosis." The electrocardiogram showed regular sinus rhythm, right axis deviation, a P-R interval of 0.20 to 0.24 second, and many junctional and ventricular premature contractions. A teleoroentgenogram showed enlargement of the heart to both sides. The urine was essentially normal. The hemoglobin was 98 per cent, with 4,800,000 erythrocytes. The total and differential leucocyte counts were normal. The blood Wassermann reaction was negative. A diagnosis of congenital heart disease, with interventricular septal defect, was made. The patient was treated with diet, limitation of fluid and salt intake, bed rest, sedatives, and digitalis. He improved rapidly and the diastolic thrill and murmur disappeared.



Fig. 1.—Case 1. Teleoroentgenogram, terminally.

Four months before death, auricular fibrillation was noted. Three months before death the patient was readmitted to the same hospital because of the reappearance of signs and symptoms of congestive failure. He had auricular fibrillation, with a ventricular rate of 76 and a blood pressure of 106/70. The physical signs were essentially the same as on the first admission, except that no diastolic thrill or

murmur was observed. Clubbing of fingers and toes with cyanosis of nail beds was present.

Fluoroscopic examination showed prominence of the pulmonary conus, dilatation of the pulmonary artery, enlargement of the inflow tract of the right ventricle, and lengthening and rounding of the left ventricle. Except for the presence of auricular fibrillation, the electrocardiogram was similar to that described above. The hemoglobin was 70 per cent and the erythrocyte count, 3,520,000. A diagnosis of rheumatic heart disease, with possible tricuspid insufficiency, was made. He improved only slightly with treatment.

Patient was transferred to Welfare Hospital two weeks before death. The physical signs were essentially the same. The cyanosis was thought to be mild; clubbing of the fingers was described. One observer believed that he could distinguish a diastolic thrill and murmur. Despite therapy, failure increased, and patient died of pulmonary edema twelve days after admission. The urine showed 1 plus albumin and an occasional leucocyte and hyaline cast. The hemoglobin was 82 per cent, with 4,020,000 erythrocytes. The total and differential leucocyte counts were normal. The urea nitrogen was 14.6 mg. per cent. Roentgenographic and electrocardiographic examination showed nothing new.

Autopsy was performed sixteen hours after death. There were definite clubbing of the fingers and toes, moderate edema of the lower extremities, and ascites (4,100 c.c.).

There was a chronic, progressive, tuberculous process in the upper lobes of both lungs, with fibrosis, caseation and cavitation, and bronchogenic spread to the right lower lobe.

The liver weighed 1,700 grams. The capsule and cut surface revealed fine nodules which averaged 3 mm. in diameter. The microscopic diagnosis was cardiac cirrhosis.

The spleen weighed 310 grams, and was intensely engorged. The pancreas was normal grossly, but, microscopically, revealed the atrophy of the peripheral portions of the lobules which is characteristic of long-standing congestion.

The heart weighed 970 grams; there were dilatation and hypertrophy of all four chambers, but both the hypertrophy and dilatation were more marked on the right. The pericardium was thickened, and the pericardial space was almost completely obliterated by thin, fibrous adhesions. No fresh fibrinous exudate was noted grossly. The myocardium of all four chambers, especially the right ventricle, was thickened. The right ventricular wall was 2.0 cm. thick at the base, 1.5 cm. midway to the apex, and 0.9 cm. at the apex. The left ventricular wall was 1.5 cm. thick at the base, 1.3 cm. midway to the apex, and 1.1 cm. at the apex. Section of the muscle revealed no gross evidence of fibrosis or infarction. The endocardium showed small patches of thickening throughout. There was a defect, about 4 by 3 cm. in size, in the most basal portion of the interventricular septum. The aorta was so situated that approximately one-third of its lumen lay above the right ventricle and two-thirds above the left ventricle. The tricuspid ring was 13.5 cm. in circumference. The valve leaflets were thickened and deformed, with shortening, thickening, and fusion of the chordae tendineae. In one area, the fusion of the chordae tendineae had resulted in fenestration at the margin of one of the leaflets. The appearance suggested that stenosis (?) and insufficiency had been present. A thin sheet of tissue resembling normal valve leaflets (in contrast to the thickened leaflets which were actually present), with chordae tendineae at its edges, was found. It was attached superiorly to the base of the aorta, and ran transversely from one of the tricuspid leaflets, parallel with the septal defect. It may have, in part, occluded the opening in the septum, as well as blocked off the lumen of the aorta from the right ventricle. The pulmonic valve was bicuspid. The leaflets were very markedly thickened and sclerotic. The orifice was 5.5 cm. in circumference, and of narrow ellipsoid shape. Deep within both sinuses there were fibrotic nodules which appeared to be acquired, rather

than congenital lesions. The pulmonary conus was narrowed and hypoplastic, and the lower orifice (3.5 cm. below the valve edge) measured 7 cm. in circumference and was circular in shape. The wall of the conus was considerably thickened and opaque.

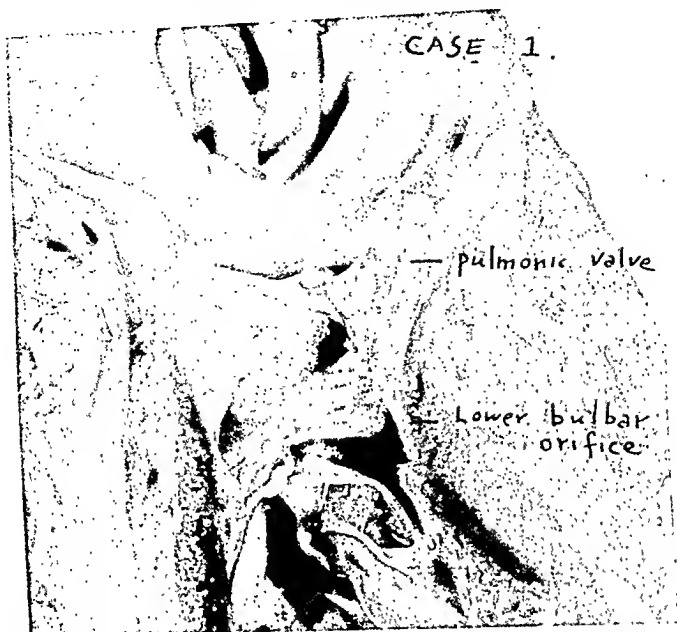


Fig. 2.—Case 1. Pulmonary conus.

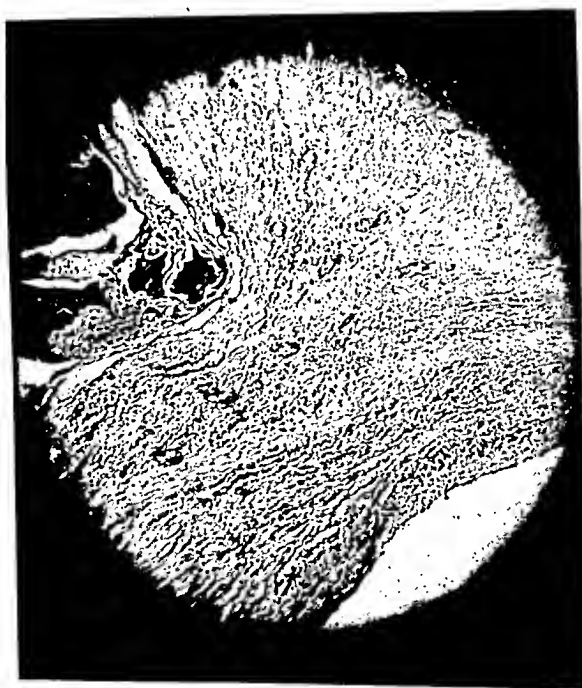


Fig. 3.—Case 1. Section of tricuspid valve.

The pulmonary artery was somewhat dilated. The mitral valve was thin and showed no gross fibrosis. The ring was 11 cm. in circumference. The aortic valve was likewise entirely normal. The aortic ring measured 9 cm. The coronary orifices were widely patent. The coronary arteries showed minimal atherosclerotic changes. Both the left descending and circumflex branches were larger than the right coronary.

The right coronary was particularly small, but its marginal branch was somewhat larger than would have been expected. No narrowing or occlusions were noted. The aorta showed a moderate degree of atherosclerosis. The measurements of the heart were made after fixation.

Microscopic Description of Heart.—The pericardium consisted of a very thick layer of fibrous and areolar tissue. It was very richly vascularized, and contained a great many small capillaries with swollen endothelial cells, and many larger congested vessels with thickened walls. In a few isolated areas there was a slight diffuse lymphocytic accumulation. Some hyaline changes were noted in the pericardium over the auricles. Some of the muscle bundles of the myocardium were hypertrophied, and others were atrophied. There was a diffuse increase in interstitial fibrous tissue which, in some areas, was rather marked. Some increase of fibrous tissue immediately surrounding blood vessels was noted. In several areas there were perivascular accumulations of lymphocytes and monocytes, with fibrillation of collagen. No Aschoff bodies were seen. The endocardium was somewhat thickened, especially in the auricles. The wall of the pulmonary conus consisted of a very thick layer of fibrous connective tissue, part of which was hyalinized. In some portions of this tissue there was a moderate accumulation of mononuclear cells, apparently fibroblasts, lymphocytes, monocytes, and plasma cells. Many congested capillaries were present. Sections of the pulmonic valve revealed that it was considerably thickened and deformed. In some areas there was evidence of hyalinization, calcification, vascularization, and lymphocytic cellular infiltration. The elastic tissue stain revealed a loss of all organized elastic tissue throughout the valve, including the nodular structures at the base. A similar process was present in the tricuspid valve, where the cellular infiltration was perhaps more intense. The aortic valve showed some calcification, without vascularization or cellular infiltration. The mitral valve contained some calcific deposits at the base, but showed no cellular infiltration or vascularization.

CASE 2.—The patient was 43 years old at the time of death. She recalled having been told that at birth she had been a "blue baby." In childhood she would become dyspneic and cyanotic on moderate exertion. A history suggestive of rheumatic infection could not be elicited. At the age of 14 years, an operation was performed for Pott's disease. The patient was hospitalized for mild congestive failure at the age of 25 years, and repeatedly thereafter. Digitalization was started at the age of 34 years. When she was 41 years of age she had a cerebral accident which left her with left-sided hemiplegia.

At the age of 43 years, the patient was admitted to this hospital because of congestive failure. Physical examination revealed a chest deformity associated with kyphosis of the spine, resulting in an increase in the anteroposterior diameter. The degree of dilatation of the veins, pulmonary congestion, hepatic engorgement, and peripheral edema varied during her hospital stay. The heart was thought to be enlarged; the point of maximal impulse was felt at the fifth intercostal space just outside the midclavicular line. A diffuse systolic thrill was present over the entire precordium, but was most marked at the apex. A harsh, rough, loud murmur, extending through systole and most of diastole, was present over the entire precordium; it was maximal at the fourth intercostal space just to the left of the sternum. The rhythm was regular, and the rate averaged 86. The blood pressure ranged from 180/130 to 230/160. Cyanosis was not present except during attacks of failure.

Her course was characterized by attacks of transient coma, associated with vague neurologic changes and described as hypertensive encephalopathy and congestive failure of varying degree. The failure at first responded to digitalis and diuretics. The patient was discharged from the hospital two months before death, only to return, on the day prior to death, with coma and severe failure.

The hemoglobin was 98 per cent, the erythrocyte count, 4,950,000; the total and differential leucocyte counts were normal. The urine concentrated to 1.016 and contained 4 plus albumin. Terminally, occasional leucocytes, erythrocytes, and casts were noted. The urea clearance was 38 per cent of normal. The phenolsulfonphthalein excretion was 15 per cent in two hours; the serum albumin was 4.4, and the globulin, 1.5; the nonprotein nitrogen on admission was 43, and, terminally, 72; the carbon dioxide combining power terminally was 14.5. A roentgenogram revealed that the heart was enlarged in all diameters. The electrocardiogram revealed right axis deviation and incomplete auriculoventricular block; the latter was caused by digitalis.

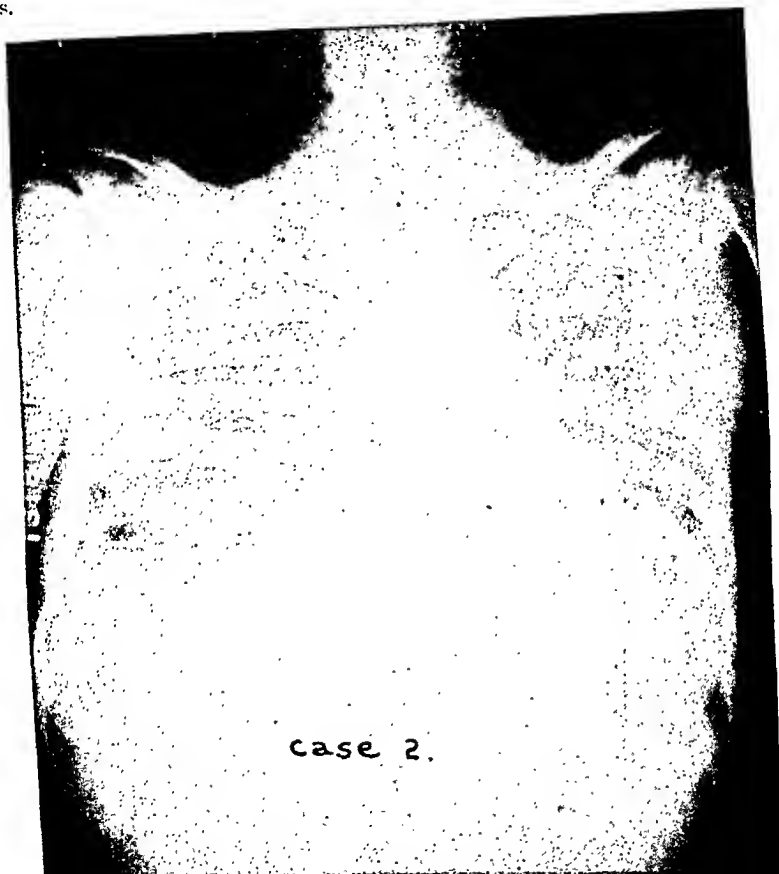


Fig. 4.—Case 2. Teleoroentgenogram, terminally.

At autopsy, clubbing of the fingers and toes and edema of the extremities were present. Examination of the brain revealed heterotopia of gray matter in the right centrum semiovale which was congenital. The lungs were congested, and, microscopically, terminal lobular pneumonia was found. The intestinal mucosa, spleen, and liver were congested. Microscopically, the liver showed the central fibrosis, atrophy, and congestion indicative of cardiac cirrhosis. The kidneys were small, with a finely granular surface and a narrowed cortex. The pelves were normal. Microscopically, the most significant change was marked arteriolar sclerosis, associated with a moderate increase in the fibrous stroma. Arteriolar thickening was noted also in the sections of liver, spleen, pancreas, duodenum, and adrenal gland.

The heart weighed 600 grams; it lay in the normal position. There were hypertrophy and dilatation of all four chambers. The pericardium was smooth and glistening. The myocardium of the left ventricle measured 20 mm. in thickness at the

base, 14 mm. midway to the apex, and 10 mm. at the apex. The myocardium of the right ventricle measured 16 mm. at the base, 14 mm. midway to the apex, and 10 mm. at the apex. On section of the myocardium, fibrous streaking was not visible grossly. The endocardial surfaces were, for the most part, smooth and glistening. An outpocketing of the interauricular septum, measuring about 2 cm., extended from the right atrium into the left. The edges of the outpocketing contained numerous small fenestrations, so that a communication between the atria existed. A valvular effect was obvious, by which these fenestrations were closed when the pressure in the left auricle exceeded that in the right. An interventricular septal defect, measuring 1.5 by 1.5 cm., was found at the most basal portion of the septum. The

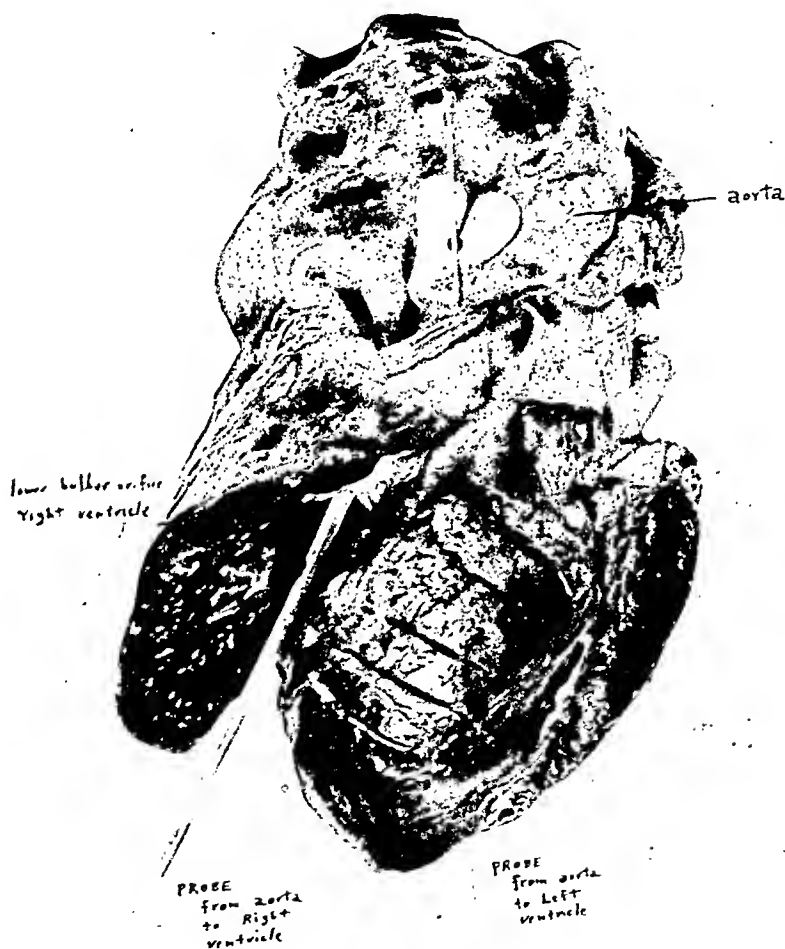


Fig. 5.—Case 2. Heart.

aorta overlay the septum, so that approximately two-thirds of its lumen was situated over the cavity of the right ventricle and one-third over the cavity of the left. The mitral, tricuspid, and aortic valves were entirely normal. The pulmonic valve was bicuspid. The valve leaflets were normal. The pulmonary artery measured 17 mm. in diameter at the valvular orifice. Beneath the pulmonic valve, the pulmonic conus was considerably thickened and fibrotic, and, at a point 15 mm. below the valve orifice, it narrowed down until it was approximately 6 by 10 mm. in diameter. The remnants of the ductus arteriosus were noted as a fibrous strand approximately 1 cm. long and 1 mm. wide, running between the aorta at a point 7 cm. above the valve orifice to the

pulmonic artery at a point 6.5 cm. above the valve orifice. No lumen could be distinguished grossly within this fibrous strand. At the site of its insertion into the aorta and pulmonary artery, small, shallow depressions were found. The coronary ostia were patent. The coronary arteries were of good caliber, and showed only slight atheromatous changes, with slight narrowing of the lumen in some areas. The aorta showed moderate atheromatous changes without ulceration or calcification. Microscopically, the ductus contained no definite lumen. The myocardium was moderately fibrotic.

COMMENT

The unusually long duration of life in the first case, 53 years, as well as the relative lack of cyanosis or decreased cardiac reserve until late in life, in spite of arduous physical labor, is, at first glance, rather difficult to understand. The heart itself provided a possible explanation for the patient's relatively good fortune. The pulmonic stenosis in this case was at the site of the valve itself. There was only slight narrowing of the lower bulbar orifice, which is the usual site for the pulmonic stenosis associated with the tetralogy. Abbott² stated that pulmonary valvular stenosis is, in these cases, "practically always inflammatory." Indeed, the appearance of the valve was characteristic of a chronic rheumatic process. We have further evidence of a rheumatic process in the pericarditis, the slight microscopic myocardial changes, the concomitant changes in the tricuspid valve, the microscopic fibrosis, and the vascularization and cellular infiltration of the valves and ventricular endocardium. Clinically, there was evidence of recurrent rheumatic infection. The conclusion seems justified that the pulmonic stenosis was, in this case, rheumatic in origin, and was probably acquired, judging from the history, some time after the age of 37 years.

Although the pulmonic stenosis was acquired, the other changes, specifically the interventricular septal defect and the dextroposition of the aorta, were manifestly congenital. This complex of congenital cardiac abnormalities, which differs from the tetralogy of Fallot fundamentally only in the absence of pulmonic stenosis, has been called the Eisenmenger complex,⁴ and is considered by some as a variant of the tetralogy. It is much less common than the tetralogy, and, what is more important, the functional changes associated with it are of less serious prognostic significance. The difference in the cardiodynamics is as indicated in Figs. 6 and 7 (adapted from Abbott).

Fundamentally, the difference lies in the fact that, in the tetralogy, the pulmonic stenosis impedes the flow of venous blood into the pulmonary artery, forcing it, instead, to pass through the septal defect into the systematic circulation. This mechanism is lacking in the Eisenmenger complex. Much less venous blood passes into the aorta, directly or by way of the septal defect; a greater portion enters the relatively wide orifice of the pulmonary artery to be oxygenated in the lungs; less cyanosis is observed and, in general, the cardiodynamics more nearly approach the normal. The relatively large size of the pulmonary artery

in this case would further indicate that at some time a relatively large volume of blood had passed through it. If the pulmonic stenosis had been present since birth, the pulmonary artery would possibly have been small and hypoplastic, as it is in the typical tetralogy. Of course, other influences may well be related to the hypoplasia which occurs in such cases.

In retrospect, we believe that this man was born with what is commonly called the Eisenmenger complex. During the early portion of his life he suffered only the relatively minor cardiac embarrassment caused by this type of lesion. At a later date a rheumatic infection supervened, with resultant stenosis of the pulmonic valve. With the development of this pulmonary stenosis, all of the anatomic changes of the tetralogy of Fallot were established, and this was accompanied by a serious derangement in cardiodynamics. This contributed to his disability and death.

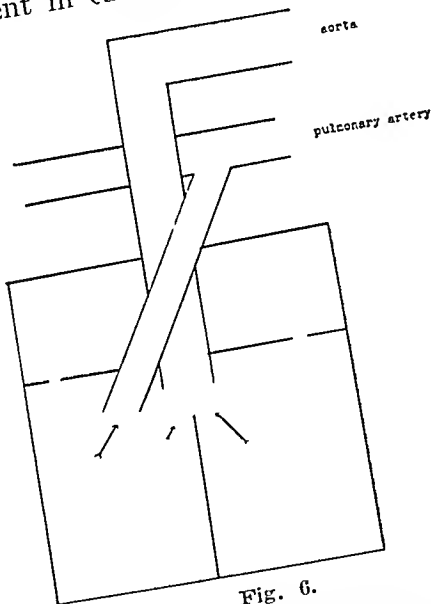


Fig. 6.

Fig. 6.—Case 1. Diagram. Circulation in Eisenmenger complex before rheumatic involvement.

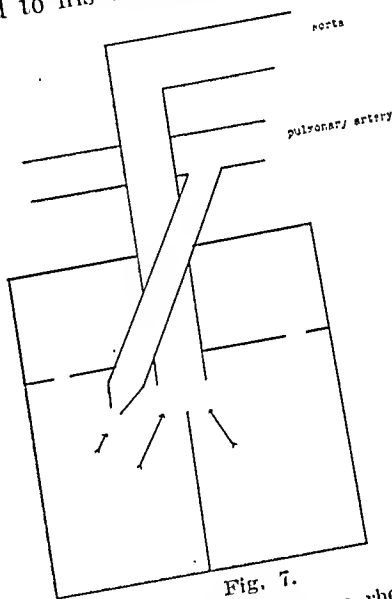


Fig. 7.

Fig. 7.—Case 1. Diagram. Circulation in tetralogy of Fallot after rheumatic involvement.

Active pulmonary tuberculosis is not rare in such cases. Norris and Landis⁵ reported that 160 of 440 patients with pulmonary stenosis, or 35 per cent, had active pulmonary tuberculosis at the time of death. In contradistinction, it is well known that patients with mitral stenosis have a comparatively low incidence of pulmonary tuberculosis.

The localization of the rheumatic infection in the right side of the heart in this case is of considerable interest. Its significance, however, is beyond the scope of this paper.

The second patient did not fare as well, either as to duration of life or symptoms. Nevertheless, there is no question that she was more fortunate than the average. One possible explanation for her relatively long life is suggested by the presence of the fibrosed remains of the

ductus arteriosus. Certainly, at the time of her death, and during the period when the ductus was fibrosed, it played no part in the altered dynamics. However, the persistence of the ductus to this age, even as a fibrous band, suggests the possibility that it might have remained patent after birth for a longer than normal period of time. While it was patent, and to the extent that it was patent, the ductus arteriosus served to alleviate the altered cardiodynamics by circumventing the stenotic pulmonary passage and permitting a greater volume of blood to enter the lungs. This is indicated in Fig. 8.

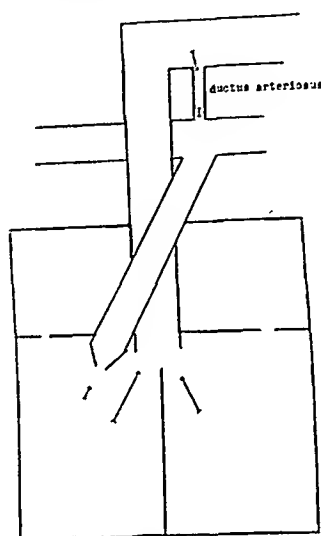


Fig. 8.—Case 2. Diagram. Effect of patency of ductus arteriosus on the circulation in the tetralogy of Fallot in early life (postulated).

Another factor which may have influenced the cardiodynamics is the systemic hypertension. This, in all probability, was the result of an unrelated acquired disease affecting the peripheral resistance, and bore no or little direct relation to central cardiac factors. The arteriolar lesions in the kidney were such as are ordinarily found in hypertension of vascular origin. In any case, the presence of increased pressure in the arteries and aorta would serve to increase the pressure within both the left and right ventricles (because of the marked dextroposition and the septal defect), at least during systole, and would thus increase the head of pressure at the narrowed pulmonic orifice. This would increase the flow of venous blood to the lungs. If the ductus arteriosus was patent, the passage of blood to the lungs would have been further facilitated. The presence and degree of systemic hypertension would tend to increase oxygenation of the blood and thus aid the patient.

The role of the patent foramen ovale is of questionable significance. The actual orifice was small, and the endocardial septa were so arranged as to possess a valvular action by which blood was permitted to pass only from right to left. In the normal heart, the pressure is somewhat greater in the left atrium than in the right. If this were true in this case, no

blood flow would occur. The decreased blood flow to the lungs, and therefore the decreased blood flow to the left auricle, may have resulted in a decrease or even a reversal in this pressure relationship. Congestive failure in this case would almost certainly have done so, and, therefore, we may assume that a small amount of blood did pass through the foramen ovale from the right to the left atrium, at least under some circumstances. This blood would then pass into the left ventricle rather than the right. The difference, however, is considered to be of only slight significance, inasmuch as the volume of blood under discussion is small, and the difference in the ultimate pathway of the blood from the two ventricles, conjoined as they were by a septal defect and a common (dextroposed) aorta, was also slight.

Roentgenologically, the tetralogy⁶ is characterized by the small size of the hypoplastic conus, associated with narrowing of the lower bulbar orifice. The roentgenogram of the second patient (Fig. 4), although not characteristic, was of this general nature. It showed changes of the hypertensive type. The roentgenogram (Fig. 1) of the first patient showed the prominence of the pulmonic conus which is characteristic of the Eisenmenger complex.

SUMMARY

Two cases are presented, in which, at autopsy, there were changes in the heart which compose the tetralogy of Fallot, namely, right ventricular hypertrophy, pulmonic stenosis, interventricular septal defect, and dextroposition of the aorta. The patients were 53 and 43 years of age, respectively. The first, it is believed, originally had an Eisenmenger variant, with no pulmonic stenosis. Rheumatic pulmonic valvulitis, acquired late in life, resulted in pulmonic stenosis, completing the tetralogy and contributing greatly to his disability and death. The second patient had the true tetralogy from birth. The presence of patency of the ductus arteriosus, and, later, of systemic hypertension, may have helped alleviate the cardiodynamic derangement and contributed to her longevity.

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MYOCARDIAL INFARCTION INDICATED BY AN ELECTROCARDIOGRAPHIC PATTERN IN WHICH T_1 IS LOWER THAN T_3

REPORT OF 45 CASES

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MYOCARDIAL infarction is signified in the electrocardiogram by a high take-off of the S-T segment and later by inversion of the T wave. These signs may be accompanied by changes in the size and shape of the QRS complex. In the presence of anterior wall infarction, the significant changes appear in Lead I. They are often associated with reciprocal changes in Lead III; that is, elevation of the S-T segment and inversion of the T wave in Lead I may be accompanied by depression of the S-T segment and by an upright T, which is sometimes of unusual height, in Lead III. The reciprocal changes do not always parallel the significant changes; they are often less pronounced or may be absent. Even then, high take-off of the S-T segment and inversion of T in Lead I are sufficient evidence of anterior wall infarction.

The interest of clinicians has been focused mainly upon the significant changes. In some instances of anterior wall infarction, however, the signs in Lead I are poorly developed or occur rather late. The elevation of the S-T segment may be inconspicuous or absent; and, instead of sharp inversion, there is sometimes but slight flattening of the T wave, which remains upright or becomes isoelectric. The flat, upright T_1 may display a slight central dip, so that an M-shaped T wave results,¹ or the dip may appear at the end of the positive T wave. When the significant changes are poorly developed, the reciprocal alterations in Lead III are often marked and predominant. A distinct depression of the S-T segment is sometimes noted in Leads II and III in the absence of elevation of S-T in Lead I. More often, the prominent change is an increase in the voltage of T_2 and T_3 .

The diagnostic significance of the reciprocal changes has received but scant attention. Zwillinger² has expressed the opinion that an isoelectric T_1 , associated with a positive T_2 and T_3 , may signify anterior wall infarction. Ashman and Hull³ have pointed out that sharp reduction in the height of T_1 and elevation of T_3 , together with a marked decrease in the amplitude of QRS in the standard leads, occasionally represent the only signs of anterior wall infarction. Bohning and Katz⁴ have stressed the diagnostic significance of "upright coronary T waves" in Leads II and III in the presence of anterior wall

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infarction. These T waves are mirror images of inverted coronary T waves. We, too, have occasionally found this sign useful in the diagnosis of anterior wall infarction. More numerous are the cases in which myocardial infarction is indicated merely by a reversal of the ratio of voltage of T_1 and T_3 , in the absence of inversion or marked enlargement of the T waves. Under normal conditions, except when the heart is perpendicular, T_1 is of greater amplitude than T_3 . Reversal of this ratio has, in our experience, proved to be a valuable sign of myocardial infarction.

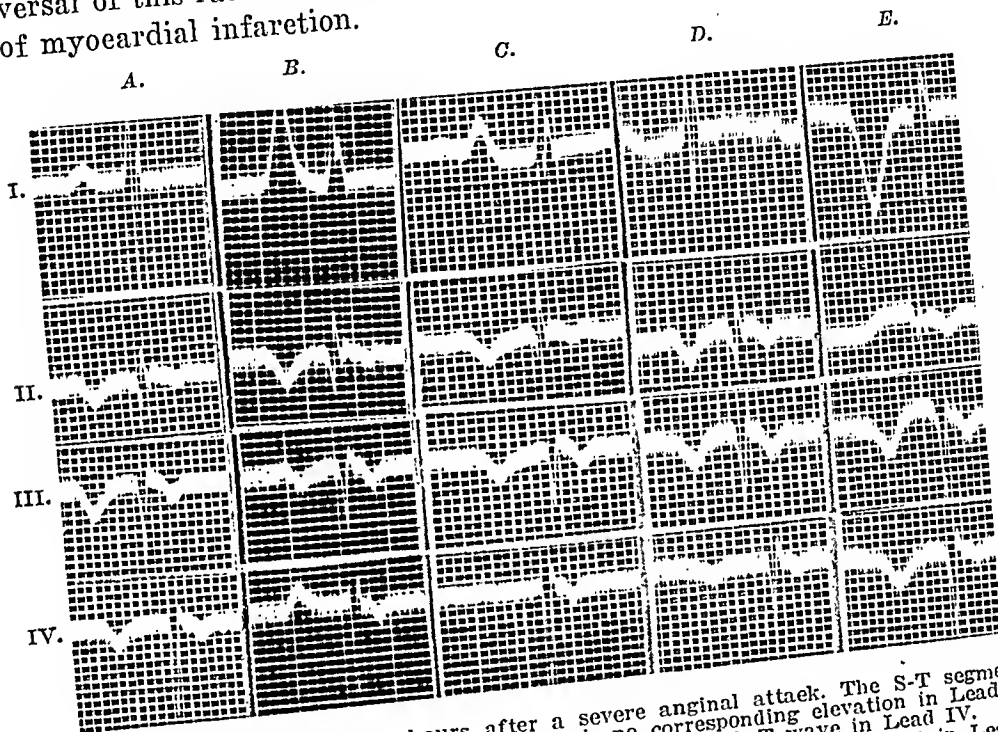


Fig. 1.—Case 1. A, Three hours after a severe anginal attack. The S-T segment is depressed in Leads II and III, and there is no corresponding elevation in Lead I. T_3 is nearly isoelectric. There is a deep Q wave and a high T wave in Lead IV. B, Thirteen hours after the attack. The depression of the S-T segment in Leads II and III has subsided. T_1 has become flatter, and T_3 upright, resulting in the pattern $T_1 < T_3$. A W-shaped QRS complex is visible in Lead IV, and T_1 is of low voltage. C, Five days after the attack. The S-T segment in Lead I is slightly convex, and a dip has appeared at the end of T_1 . There is sharp inversion of T_4 . D, Five weeks after the attack. T_1 is inverted and there is a marked increase in the voltage of the negative T_1 . E, Four and a half months after the attack. T_1 has become positive again. The inverted T_1 has decreased in voltage.

CASE REPORTS

CASE 1.—H. L., a white man, aged 50 years, had suffered from hypertension for many years. On Sept. 22, 1939, while playing cards, he was seized by severe precordial pain which radiated to the left shoulder and arm, and burst into a cold sweat. The next day he had a leucocytosis of 13,850, and his blood pressure had fallen to 90/70.

The first electrocardiogram (Fig. 1A) was taken three hours after the onset of the attack. It showed distinct depression of the S-T segment in Leads II and III, but no conspicuous elevation of S-T in Lead I. The precordial lead showed a deep Q wave and an upright T of marked amplitude. Thirteen hours after the attack (Fig. 1B), the depression of S-T in Leads II and III had disappeared; T_1 was now distinctly flattened, whereas T_3 had grown high so that reversal of the ratio of amplitude of T_1 and T_3 resulted. A W-shaped QRS complex had developed in the precordial lead, and T_4 was markedly reduced in voltage.

Five days after the attack (Fig. 1C), a slight convexity of the S-T segment and a shallow dip at the end of the T wave were noted in Lead I. The T waves in Leads II and III were upright, but not of unusual voltage. In the precordial lead sharp inversion of the T wave had developed. An electrocardiogram taken five weeks after the attack (Fig. 1D) showed distinct inversion of T_1 and a marked increase in the voltage of the inverted T wave in Lead IV. Four and a half months after the attack (Fig. 1E), the T wave in Lead I had turned positive and was equal in voltage to T_3 . A shallow, inverted T wave was visible in Lead IV.

Comment.—Myocardial infarction was indicated thirteen hours after the onset of the anginal attack by reversal of the ratio of voltage of T_1 and T_3 ; there were also significant changes in Lead IV. A remarkable feature was the initial depression of the S-T segment in Leads II and III, in the absence of a corresponding high take-off in Lead I.

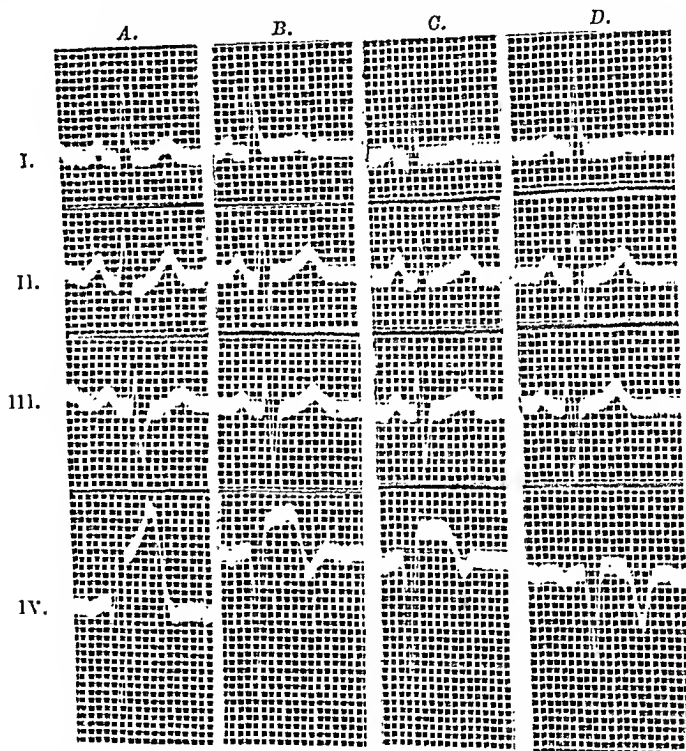


Fig. 2.—Case 2. A, On the day when the patient had suffered two severe anginal attacks. Besides left axis deviation and slurring of QRS in the standard leads, there are a high take-off of the S-T segment and marked increase in the voltage of T in Lead IV.

B, One day after the attacks. T_1 has decreased in voltage and T_3 is slightly higher, resulting in the pattern $T_1 < T_3$. The R wave has disappeared and the T wave has become inverted in Lead IV.

C, Four days after the attacks. T_1 is even more flattened.

D, Four and one-half months after the attacks. T_1 is almost isoelectric and T_3 is positive. There is sharp inversion of T_4 .

CASE 2.—C. W., a white man, aged 51 years, on Jan. 8, 1939, felt a sharp pain in the left scapular region while pulling a drunkard out of his car. On the following day a few short attacks of pain occurred. On January 10, the patient was seized by an anginal attack of greater severity; he became cyanotic and perspired profusely. On January 12, he had two more attacks of violent pain which required the administration of morphine.

The first electrocardiogram was taken January 12 (Fig. 2A). It showed, in addition to left axis deviation, slurring of QRS in the standard leads, and elevation of the S-T segment in the precordial lead. On the following day, January 13 (Fig. 2B), the T wave in Lead I had become flat, and its amplitude was less than that of T_2 . Simultaneously, the R wave in the precordial lead disappeared, and inversion of T_4 developed. In the next tracing, taken January 16 (Fig. 2C), T_1 was more flattened. Reversal of the ratio of amplitude of T_1 and T_3 was still visible in a tracing taken after four and a half months (Fig. 2D).

Comment.—Myocardial infarction was indicated twenty-four hours after the anginal attack by the electrocardiographic pattern $T_1 < T_3$, and also by significant changes in Lead IV. These signs were still present four and a half months after the attack.

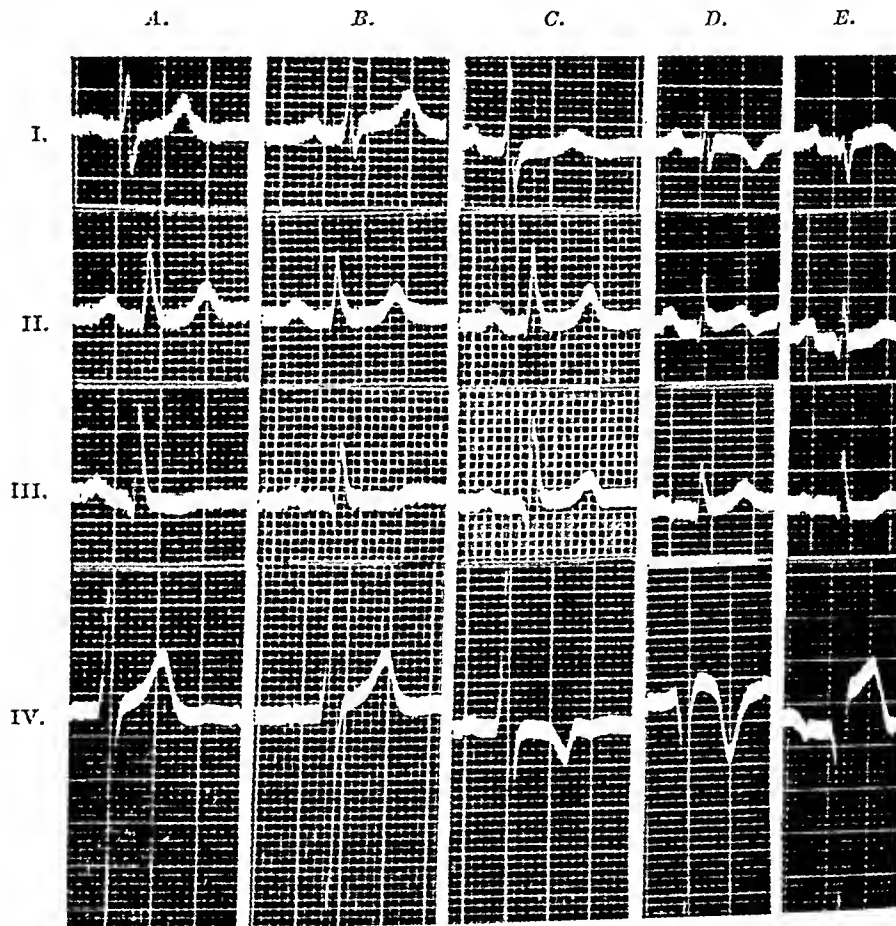


Fig. 3.—Case 3. A and B were taken at the time when the patient suffered from severe angina pectoris of effort, not of rest. There were no significant changes in the electrocardiogram.

C. Five weeks later, when the patient suffered numerous brief anginal attacks during rest, relieved by nitroglycerin. T_1 has become flattened and T_3 upright, resulting in the pattern $T_1 < T_3$; also, inversion of T_4 has developed.

D. One day after a severe, long anginal attack, followed by a pericardial friction rub. There are low voltage of QRS and slight elevation of S-T in the standard leads. T_1 is inverted. In the precordial lead, the R wave has disappeared and T_4 has become sharply inverted.

E. Two days following a fresh severe anginal attack. A large Q wave has appeared in Lead I. The S-T segment is slightly elevated in Lead I and depressed in Lead III. In Lead IV, marked elevation of S-T has developed and T_4 has become upright.

CASE 3.—B. J., a white man, aged 64 years, in February, 1932, after pushing his car, suffered an attack of severe precardial pain which lasted several hours. Myocardial infarction was diagnosed. After this attack recovery was complete, and the patient was able to walk as many as fifty blocks without experiencing discomfort.

In March, 1941, pain in the precardial region occurred again during walking; the patient was not able to walk more than two or three blocks without experiencing anginal pain. Two electrocardiograms, taken March 11 and 18, 1941 (Fig. 3A and B), failed to reveal significant abnormalities. A diagnosis of impending infarction was made. The sedimentation rate (Westergren) was 68 mm. on March 12.

Early in April, 1941, the attacks of pain grew more severe; they came on even during rest, frequently at night, and lasted from ten to twenty minutes. They were promptly relieved by nitroglycerin. The patient was advised to stay at home, but, even then, he suffered ten to twelve attacks every day. An electrocardiogram taken April 24, 1941 (Fig. 3C), showed distinct flattening of T_1 , together with an increase in the voltage of T_2 . Also, inversion of the T wave had developed in the precardial lead. In spite of complete rest in bed, protracted attacks of severe precardial pain occurred April 30, and the administration of morphine was required. A pericardial friction rub was heard on the following day. An electrocardiogram taken May 1 (Fig. 3D) showed inversion of T_1 and low voltage of QRS in the standard leads; R_1 had disappeared and inversion of T_1 was more pronounced. Another violent attack occurred May 10, and was followed by pulmonary edema. An electrocardiogram taken May 12 (Fig. 3E) displayed a large Q wave and slight elevation of S-T in Lead I; a high take-off of the S-T segment, with an upright T, was present in Lead IV. The patient died on May 22, 1941.

Post-mortem examination revealed marked arteriosclerosis of the coronary arteries. The ramus descendens anterior of the left coronary artery was occluded by an old thrombus. The right coronary artery was almost completely obstructed by calcified deposits. The apical region of the left ventricle was thinned; its muscle was replaced by whitish fibrous tissue. There were also large areas of yellowish discoloration, with hemorrhages, indicating recent infarction, in the lateral wall of the left ventricle and in the interventricular septum. Whitish streaks of fibrosis were also visible in the posterior wall of the left ventricle.

Comment.—Progressive coronary insufficiency during the last two months of life caused repeated myocardial infarctions, as shown by necropsy. The second phase of the disease, initiated by brief anginal attacks during rest, was characterized in the electrocardiogram by reversal of the ratio of amplitude of T_1 and T_2 (Fig. 3C).

CASE 4.—S. M., a white woman, aged 60 years, was admitted to the hospital September 26, 1941, after she had suffered brief attacks of precardial pain during rest, for six weeks. Examination revealed marked hypertrophy of the left ventricle, as indicated by a broad, heaving apex beat. The heart sounds were fair, and no bruits were audible. During the first few days after admission the temperature rose to 100.2° F. The blood pressure, which had previously been high, according to the history, measured 136/74 on admission. The leucocyte count was 10,600 on September 27. The sedimentation rate (Westergren) was 23 mm.

An electrocardiogram on September 29 (Fig. 4A) showed, besides left axis deviation, an almost isoelectric T in Lead I; an upright T wave of high voltage, exhibiting the features of the "upright coronary T waves," was present in Leads II and III. T_1 was inverted. During the following three weeks three electro-

cardiograms were taken (Fig. 4B, C, and D); they showed only slight variations. T_1 became temporarily negative (Fig. 4C). Reversal of the ratio of voltage of T_1 and T_3 remained the predominant feature of the electrocardiogram.

Comment.—The history of repeated anginal attacks during rest, and the rise in temperature, leucocytosis, and increased sedimentation rate indicated myocardial infarction. In the electrocardiogram this diagnosis was supported by the pattern $T_1 < T_3$, and by inversion of T_4 .

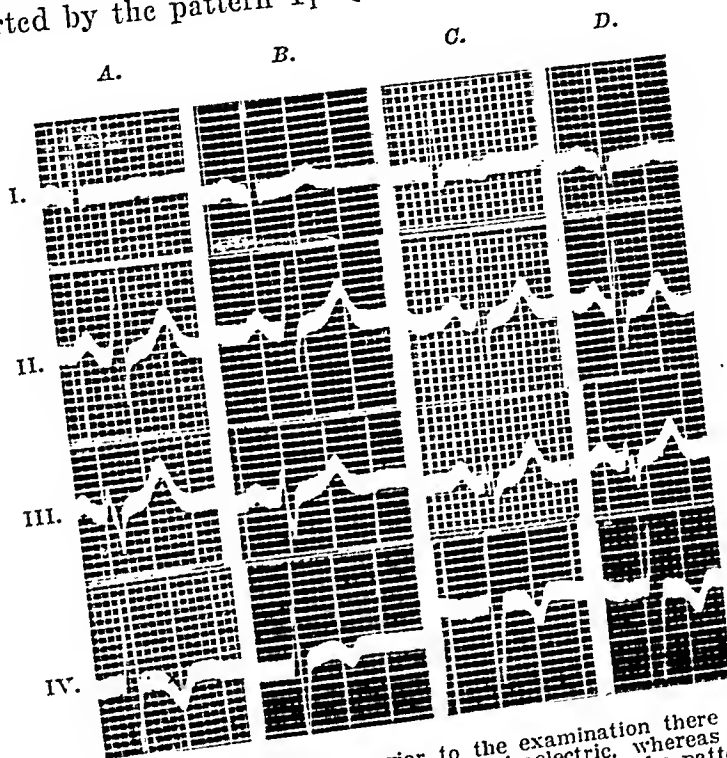


Fig. 4.—Case 4. A, For six weeks prior to the examination there were numerous brief anginal attacks during rest. T_1 is almost isoelectric, whereas T_2 and T_3 are upright and high ("upright coronary T waves"), resulting in the pattern $T_1 < T_3$. T_4 is inverted.

B, after seven days, T_1 is upright and still smaller than T_3 .

C, after nineteen days, T_1 has become inverted.

D, after twenty-one days, T_1 is upright again; the pattern $T_1 < T_3$ is still present.

CASE 5.—H. R., a white man, aged 60 years, had suffered from substernal pain since the middle of 1941. The attacks came on while he was walking, and subsided after a few minutes of rest. In August, 1941, the patient was seized by severe precordial pain which lasted for a few days. He was hospitalized, and myocardial infarction was diagnosed. In December, 1941, the patient again suffered several anginal attacks at night, each lasting about ten minutes. The sedimentation rate was 50 mm. (Westergren) on December 13. An electrocardiogram (Fig. 54), on December 12, showed low voltage of QRS in the standard leads; T_1 was nearly isoelectric, and T_2 and T_3 were positive and high. The T wave in the precordial lead was sharply inverted.

Comment.—The history of repeated attacks of severe anginal pain during rest suggested past and recent myocardial infarction. The electrocardiographic pattern $T_1 < T_3$, associated with low voltage of QRS and inversion of T_4 , supported this diagnosis.

CASE 6.—A. S., a white man, aged 52 years, in 1934 had had an attack of severe precordial pain during rest, associated with a fainting feeling, cold sweat, and vomiting. Two injections of morphine were required, and the patient was hospitalized. Thereafter, anginal pain was often felt on exertion and occasionally during rest. When the patient was first examined by us on Nov. 7, 1939, his electrocardiogram (Fig. 5C) showed upright T waves in the standard leads; T_1 was lower than T_2 . In the precordial lead a W-shaped QRS complex was noted, and the T wave was diphasic. Two other tracings, taken May 17, 1940 (Fig. 5D), and Dec. 2, 1940 (Fig. 5E), showed the same reversed ratio in the voltage of the T waves in Leads I and III. T_4 in the last tracing was sharply inverted.

Comment.—Myocardial infarction which, according to the history, had been sustained six years earlier, was indicated in the electrocardiogram by the pattern $T_1 < T_2$, and by significant changes in the precordial lead.

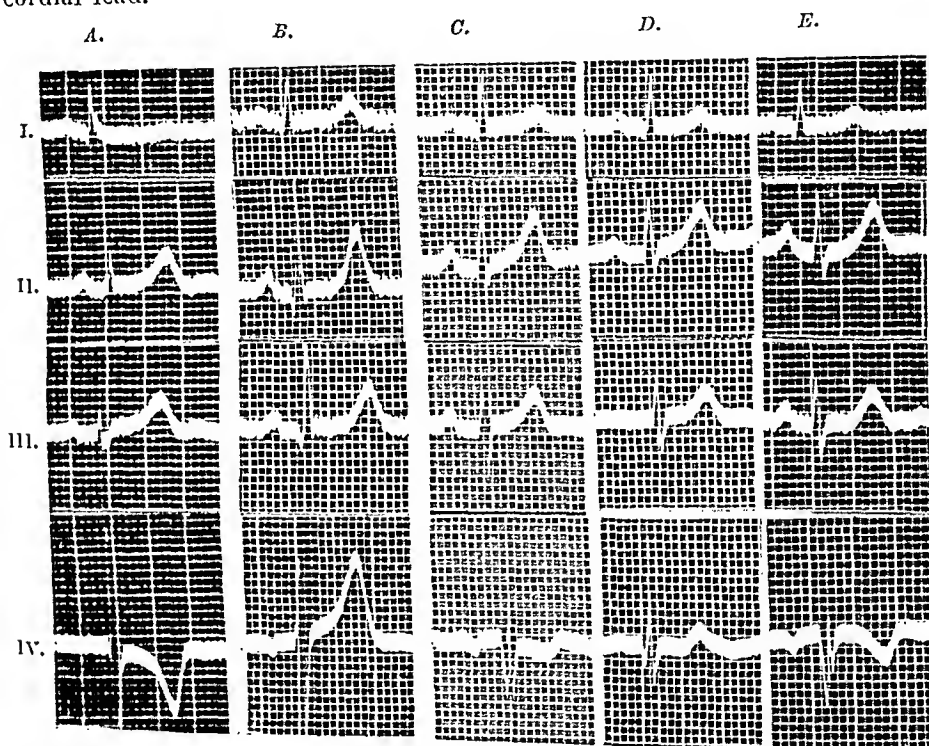


Fig. 5A.—Case 5. After repeated severe anginal attacks. T_1 is almost isoelectric. T_2 and T_3 are upright and rather high, resulting in the pattern $T_1 < T_2$. T_4 is sharply inverted. There is low voltage of QRS in the standard leads.

Fig. 5B.—Case 7. Sixteen years previous to the examination the patient had suffered a severe anginal attack, with collapse. All T waves are upright. T_1 is of normal voltage, but T_2 and T_3 are abnormally high ("upright coronary T waves"), resulting in the pattern $T_1 < T_2$. The precordial lead is normal.

Fig. 5C, D, and E.—Case 6. Six years prior to examination there was an attack of severe precordial pain, with faintness and collapse. All three tracings (C, D, and E), taken at intervals of about six months, show the pattern $T_1 < T_2$. In the precordial lead there are significant changes; QRS is W-shaped and the T wave diphasic (in E).

CASE 7.—D. R. was a white man, 70 years of age. Sixteen years earlier, while walking in the street, he suddenly felt a severe pain substernally and collapsed. Thereafter, he was confined to bed for six weeks. The patient had to give up his work because he frequently suffered anginal pain on exertion and occasionally even during rest. The pain was promptly relieved by nitroglycerin.

TABLE I

ANALYSIS OF 45 CASES IN WHICH THERE WAS THE ELECTROCARDIOGRAPHIC PATTERN $T_1 < T_3$,
WITH SYMPTOMS AND SIGNS SUGGESTIVE OF MYOCARDIAL INFARCTION

CASE	AGE	SEX	ANGINA PECTORIS OF EFFORT	SYMPTOMS AND SIGNS SUGGESTING MYOCARDIAL INFARCTION	ELECTROCARDIOGRAM		COMPLICATING CONDITIONS	NECROPSY OBSERVATIONS
					T_1/T_3 VOLTAGE IN MM.	OTHER CHANGES		
1. H. L.	50	♂		Attack of severe precordial pain with cold sweat, followed by leucocytosis and fall in blood pressure	1.1/3.0	Progressive changes. Temporary inversion of T_1 . W. shaped QRS and inversion of T in Lead IV	Hypertension	
2. C. W.	51	♂		Several severe attacks of anginal pain requiring morphine	0.8/2.0	Progressive changes. Elevation of S-T, absence of R and inversion of T in Lead IV		
3. B. J.	64	♂	6 weeks	Repeated attacks of severe and protracted anginal pain, followed by rise in temperature and increased sedimentation rate	1.4/2.0	Progressive changes significant of anterior wall infarction		Fibrosis and thinning of the apical region of the left ventricle. Recent infarction in the interventricular septum and lateral wall of the left ventricle. Areas of fibrosis in the basal portion of the posterior wall of the left ventricle
4. S. M.	60	♀		Repeated brief attacks of precordial pain occurring at rest, followed by precordial tenderness, rise in temperature, leucocytosis, and increased sedimentation rate	0.3/4.0	Transient inversion of T_1 . Inversion of T_4 . "Upright coronary T waves"		

5. H. R.	60	♂	6 months	Severe attack of precordial pain, followed by increased sedimentation rate. Patient was admitted to a hospital where anterior wall infarction was diagnosed	0.5/3.4	Sharply inverted T _i		
6. A. S.	52	♂	6 years	Attack of severe precordial pain, with collapse, cold sweat, and vomiting	1.2/3.8	W-shaped QRS and inversion of T in Lead IV		
7. D. R.	70	♂	16 years	Attack of severe precordial pain, with collapse. Patient was then confined to bed for 6 weeks	2.0/4.0	"Upright coronary T waves" in Leads II and III	Intermittent claudication	
8. M. L.	73	♂		Within 20 months four attacks of precordial pain, lasting up to 20 hours, and followed by rise in temperature and increased sedimentation rate	2.0/2.8	Diphasic (minus-plus) T wave of low voltage in Lead IV		
9. S. S.	59	♂	6 years	Long attack of severe precordial pain with cold sweat	0/1.5	Progressive changes. Temporary inversion of T _i and sharp inversion of T _i	Diabetes, hypertension, intermittent claudication	
10. S. G.	47	♂	1½ years	Attack of sharp precordial pain, with subsequent, lasting fall in blood pressure	1.0/2.0	Progressive changes. Elevation of S-T and sharp inversion of T in Lead IV		
11. S. K.	62	♂		Attack of severe precordial pain, not relieved by morphine, and lasting for 2½ days	2.0/2.8			
12. A. K.	55	♂	13 months	Attack of severe precordial pain, followed by confinement to bed for 12 weeks	0.7/1.3	Progressive changes. Temporary inversion of T _i . W-shaped QRS and inversion of T in Lead IV		
13. D. B.	54	♂		Repeated attacks of pain in the epigastrium and beneath the sternum, the last attack followed by rise in temperature and drop of blood pressure	0/2.0			

TABLE I—CONT'D

CASE	AGE	SEX	ANGINA PECTORIS OF EFFORT	SYMPTOMS AND SIGNS SUGGESTING MYOCARDIAL INFARCTION	ELECTROCARDIOGRAM		COMPLI- CATING CONDITIONS	NECROPSY OBSERVATIONS
					T ₁ /T ₃ VOLTAGE IN MM.	OTHER CHANGES		
14. S. R.	56	♂	6 years	Severe attack of precordial pain, with profuse perspiration, lasting for one hour. Morphine was given and patient was confined to bed for 6 weeks	0.8/2.0	Diphasic (minus-plus) T wave of low voltage in Lead IV		
15. F. L.	60	♀	8 weeks	Nocturnal attacks of violent precordial pain, followed by increase in sedimentation rate	1.4/2.2	S-T depressed and upright T of low voltage in Lead IV		
16. M. S.	65	♀	2 years	Attack of violent precordial pain lasting for 2 hours, followed by increased sedimentation rate	1.0/1.5	Diphasic (minus-plus) T wave of low voltage in Lead IV	Hyperten- sion	
17. J. B.	70	♂		Attack of severe pain in the precordium and epigastrium, followed by repeated attacks of burning pain which were relieved by belching. Increase in sedimentation rate	0.7/1.2		Hyperten- sion	
18. W. L.	50	♂		Severe substernal and epigastric pain, with cold sweat following an automobile accident	0/2.0	Low voltage of QRS in Lead I. Conspicuous Q ₂ and Q ₃		Coronary arterio- sclerosis. Old healed infar- ction in the apical area and anterior wall of the left ven- tricle. Scat- tered areas of fibrosis through- out the myocar- dium
19. M. F.	53	♂		Several attacks of precordial pain, each lasting for a few hours, within the preceding 2 years	0.8/2.0			

20. E. C.	65	♂		For the preceding 2 months, slight effort caused marked shortness of breath. The patient had always been well previously, and was accustomed to hard work.	0/1.2	Low voltage of QRS in the three standard leads. Absence of R and inversion of T in Lead IV		
21. H. G.	63	♂		Two weeks after an abdominal operation, repeated attacks of severe precordial pain occurred during rest, followed by rise in temperature and increased sedimentation rate.	1.5/2.0	Progressive changes. Flattening of T ₁ which finally turned diaphasic		
22. N. W.	47	♂	1 year	Attack of precordial pain, with collapse; pain lasted for 24 hours	0.8/2.0	Low voltage of QRS in Lead I.	Hypertension	
23. H. P.	60	♀	2 years	Attack of violent precordial pain lasting a whole night	0.8/2.0	Sharp inversion of T ₁		
24. J. G.	43	♂	2 years	Following a cold, sharp precordial pain developed, lasting for 2 hours, followed by rise in temperature	0.7/1.3	Significant Q ₁ ; W-shaped QRS and inversion of T in Lead IV		
25. H. J.	51	♂		Attack of severe pressure in the precordium, with collapse and cold sweat, followed by increased sedimentation rate	0.5/4.0	Sharp inversion of T ₁		
26. B. S.	59	♂	1 year	Attack of exerting precordial pain, requiring morphine, followed by rise in temperature	0.8/3.0	Progressive changes. Temporary inversion of T ₁ . Absence of R and inversion of T in Lead IV	Intermittent claudication	
27. M. D.	52	♂		Repeated attacks of sharp precordial pain of 15 minutes' duration for 2 weeks	0.5/3.0	Sharp inversion of T ₁		
28. J. Z.	55	♂	1 year	Attack of violent, constricting chest pain lasting several hours, with vomiting	0.8/2.5	W-shaped QRS and inversion of T in Lead IV		
29. J. K.	51	♂	2 years	Attack of severe precordial pain lasting several hours, followed by rise in temperature	0/1.8	Absence of R, elevation of S-T, and beginning inversion of T in Lead IV		

TABLE I—CONT'D

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CASE	AGE	SEX	ANGINA PECTORIS OF EFFORT	SYMPTOMS AND SIGNS SUGGESTING MYOCARDIAL INFARCTION	ELECTROCARDIOGRAM			COMPLICATING CONDITIONS	NECROPSY OBSERVATIONS
					T ₁ /T ₂ VOLTAGE IN MM.	OTHER CHANGES			
30. E. P.	49	♂	4 years	Attack of severe precordial pain of 4 hours' duration, with profuse perspiration	0.5/3.5				
31. J. K.	57	♀	3 weeks	Sudden onset of severe angina pectoris of effort, 3 weeks prior to examination. The patient was not able to walk more than one block. Increase in sedimentation rate	0/3.0	Progressive changes. Sharp inversion of T ₁		Hypertension	
32. P. S.	52	♂	2 months	Attack of violent precordial pain, with cold sweat lasting ½ hour, followed by increase in sedimentation rate	0/1.3	Progressive changes. Sharply inverted T ₁			
33. B. B.	47	♂		Attack of severe precordial pain, with collapse	0.8/2.5	Progressive changes. Inversion of T ₁			
34. W. L.	48	♂	4½ months	Attack of severe precordial pain lasting 15 minutes, in two successive nights	0.7/1.3	Inversion of T ₁			
35. J. S.	52	♀	4 months	Severe effort angina, with sharp onset on a certain day. The patient was unable to walk more than ½ block. Rapid sedimentation rate	0/3.0	Progressive changes. Temporary inversion of T ₁ . Sharp inversion of T ₂			
36. J. F.	68	♂	5 months	Repeated attacks of precordial pain during rest, lasting about 15 minutes. Leucocytosis	0/1.0	W-shaped QRS and inversion of T in Lead IV			
37. S. S.	65	♂	7 years	Severe attack of precordial pain requiring morphine, followed by frequent anginal attacks. The patient was repeatedly hospitalized because of such attacks	0.3/1.5	Significant Q ₁ ; very small R ₄		Hypertension	
38. L. L.	61	♀	2 years	Prolonged attack of violent precordial pain, followed by increased sedimentation rate	0.3/1.1	Diphasic (plus-minus) T ₁		Diabetes	

39. J. A.	63	♂		Attack of severe precordial pain during rest, lasting about 15 minutes, and anginal attacks during subsequent nights, followed by leucocytosis	1.0/2.0	Absence of R and sharp inversion of T in Lead IV		
40. J. H.	45	♂		Attack of precordial pain radiating to the left arm, of several hours duration	1.0/1.3	Progressive changes. Elevation of S-T and sharp inversion of T in Lead IV	Rheumatic heart disease. Subacute bacterial endocarditis	
41. W. H.	25	♂		Attack of severe precordial pain, radiating to the left arm, lasting 24 hours	0.6/1.3	Progressive changes. Low voltage of QRS in the standard leads. Inversion of T.		
42. H. F.	49	♂		Severe pain in the precordial region and left arm, lasting 2 hours, followed by leucocytosis, rise in temperature, and increased sedimentation rate	0.4/1.2	Progressive changes. Inversion of T.	Hypertension	
43. H. J.	52	♂	1 year	Following an abdominal operation, repeated attacks of substernal pressure and numbness in both arms, with profuse perspiration. The attacks lasted about 10 minutes. Subsequently, there was rise in temperature and increased sedimentation rate	0/3.3	Progressive changes. Lowering and part inversion of T.	Hypertension	
44. B. F.	60	♀	2 years	Attack of violent precordial pain during night followed by rise in temperature, fall in blood pressure, and increased sedimentation rate	0.8/1.3	Progressive changes		
45. D. D.	71	♂	2 years	Attack of severe pain in left arm and precordium lasting several hours. Subsequently, rise in temperature, leucocytosis, and increased sedimentation rate	0.3/2.0	Progressive changes. Lowering and part inversion of T.		

The patient was admitted to the hospital in July, 1942, because of arteriosclerotic ulcerations of his toes. He did not complain of anginal pains at that time. Routine electrocardiographic examination (Fig. 5B) revealed the pattern $T_1 < T_3$ and "upright coronary T waves" in Leads II and III. This aroused a suspicion of myocardial infarction which was borne out by the history.

Comment.—Myocardial infarction sixteen years prior to examination was indicated in the electrocardiogram by the pattern $T_1 < T_3$.

Table I presents the clinical and laboratory data on forty-five patients who showed the electrocardiographic pattern $T_1 < T_3$ together with other evidence suggestive of myocardial infarction. Only tracings without inversion of the T waves were considered as fitting into the pattern $T_1 < T_3$. In all cases except one, a clinical diagnosis of coronary arteriosclerosis and ischemic myocardial necrosis was made. One patient (Case 41) had rheumatic heart disease and subacute infectious endocarditis. He had an attack of severe pain in the chest, followed by significant electrocardiographic changes; the attack was interpreted as due to coronary embolism. This patient was 25 years old, the youngest in our series. In the arteriosclerotic group, the ages ranged from 45 to 73 years. Thirty-seven of our patients were men, and eight were women.

All but one of the patients had a history of angina pectoris. Forty-two patients had had one or more attacks of severe precordial pain during rest; in nineteen cases, the attacks were protracted, lasting from a half-hour to a few days. Angina pectoris of the effort type was present in twenty-seven cases. In twenty-three cases, the anginal attacks were followed by a rise in temperature, leucocytosis, rapid sedimentation rate, or a fall in blood pressure, or by a combination of these signs. An increased rate of sedimentation was most frequently observed. Two patients (Cases 31 and 35) gave a history of angina pectoris of effort, but not at rest. They remembered accurately the date of onset of their pains, which were of marked intensity and occurred after walking only one block or less. According to our experience, these signs usually point to ischemic myocardial necrosis. One patient (Case 20) gave no history of angina pectoris. He complained only of marked shortness of breath that had developed suddenly two months before. Electrocardiographic examination showed the pattern $T_1 < T_3$ and absence of R_4 and inversion of T_4 .

As has been mentioned, the electrocardiographic pattern $T_1 < T_3$ was present in all cases, either during the acute phase, after severe anginal pain, or as a persistent sign of chronic, irreversible myocardial changes. T_1 was upright in thirty-two cases and isoelectric in thirteen. In two instances the upright T_1 was M-shaped, and four times its positive portion was followed by a shallow negative phase. The upright T_1 was usually of low amplitude; only in two cases was its amplitude 2 mm.; in twenty-seven cases it was less than 1 mm.; and in sixteen cases

it ranged from 1 to 2 mm. Serial electrocardiographic examination showed a negative T wave in Lead I in nine cases.

Significant changes in the QRS complex were infrequent. A Q wave of significant size was observed twice in Lead I and once in Leads II and III. Low voltage of QRS in Lead I was present in five cases; low voltage in all standard leads was noted in nine instances. None of our patients had marked intraventricular block. Slight elevation of the S-T segment in Lead I was observed in one case only. Slight depression of the S-T segment in Lead I was present in five cases; marked depression of S-T in Leads II and III was observed in four instances.

The amplitude of the positive T wave in Lead III was almost invariably above the average, which, according to various authors,^{3, 5-7} has been estimated as from minus .74 to plus 1.22 mm. In eight of our cases the amplitude of T_3 was more than 3 mm. The maximum amplitude was 4 mm. (three instances). Two patients had "upright coronary T waves" in Leads II and III.

The precordial lead was normal in nine cases. The majority of our patients showed changes in the QRS complex or T wave or both, such as usually accompany anterior wall infarction. The R wave in Lead IV was absent or of abnormally low voltage in twelve cases; in eight of these there was a W-shaped QRS complex. Abnormal elevation of the S-T segment was noted in two instances; slight depression of S-T was present in one case. The most frequently anomaly in Lead IV was inversion of the T wave (twenty-four cases); in fifteen cases, this was the only change in Lead IV. In two instances, T_4 was upright but of abnormally low voltage; in five cases, it was of low amplitude and diphasic (minus-plus).

DISCUSSION

Edeiken and Wolferth,⁸ who studied the significance of low voltage T waves in Lead I (less than 2 mm. high), have stated that the voltage of T_1 is influenced by the position of the heart and diaphragm. When the heart is vertically placed, T_1 is sometimes low in the absence of heart disease, and is then usually associated with a low R_1 . Roentgenologic study of the chest is therefore considered essential for the diagnostic evaluation of a low T_1 . When, however, a low T_1 is associated with a normal or high R wave in Lead I, this is, according to Edeiken and Wolferth, strong indication of cardiac abnormality, especially of hypertensive heart disease.

Ashman and Hidden⁹ have pointed out that the ratio of voltage of T_1 and T_3 , rather than absolute measurement, is diagnostically important. The electrical axis of QRS must be considered in the diagnostic evaluation of the ratio of voltage of T_1 and T_3 . Right axis deviation of QRS tends to be associated with right axis deviation of T ($T_1 < T_3$). This happens even in the absence of heart disease when the electrical axis of QRS forms an angle greater than plus 30°; when the angle is

less than plus 30° the pattern $T_1 < T_3$ indicates cardiovascular disease. In 80 per cent of such cases, as observed by Ashman and Hidden, right axis deviation of T was associated with hypertensive arteriosclerotic heart disease, and, in 10 per cent, with cardiovascular syphilis. It was rarely noted with other conditions, such as thyrotoxic heart disease (2.5 per cent), rheumatic heart disease (2 per cent), congenital heart disease (0.4 per cent), nephritis (0.8 per cent), and anemia (0.4 per cent).

Of our group of cases the pattern $T_1 < T_3$ was associated with dependable evidence of myocardial infarction in 75 per cent (thirty-four cases). As dependable evidence we have considered (1) protracted attacks of anginal pain, followed by a rise in temperature, leucocytosis, increased sedimentation rate, or a fall in blood pressure; (2) progressive electrocardiographic changes after attacks of anginal pain; and (3) absence or abnormally low voltage of R_4 , associated with inversion of T_4 . In two of our cases in which necropsy was obtained, there was evidence of old and recent infarction of the left ventricle, involving mainly the anterolateral wall and the interventricular septum. Necropsy observations, however, did not yield conclusive evidence as to the diagnostic significance of the electrocardiographic pattern $T_1 < T_3$, for the pathologic process underlying that pattern did not usually lead by itself to a fatal outcome. Death was the result of new, superimposed pathologic events which caused additional changes in the electrocardiogram, such as a deep Q wave, or high take-off of the S-T segment and inversion of T. In one case, reported by Zwillinger,² post-mortem examination revealed anterior wall infarction; the only electrocardiographic anomaly was an isoelectric T_1 , accompanied by a positive T_3 .

In eleven cases (25 per cent) of our series there was no dependable evidence of myocardial infarction; this possibility, however, was suggested by a history of severe angina pectoris of effort and at rest, and often by the presence of an inverted T wave in the precordial lead. Thus, the evidence seems to indicate that in the majority, if not in all, of our cases, recent or past myocardial infarction was the cause of the electrocardiographic pattern $T_1 < T_3$. The frequent coincidence of this pattern with electrocardiographic changes in the precordial lead indicative of anterior wall infarction suggests that the pattern $T_1 < T_3$ is probably equivalent to the T_1 type of myocardial infarction.

Reversal of the ratio of voltage of T_1 and T_3 is probably not caused by extensive myocardial necrosis. Death never occurred, as has been mentioned, immediately after the development of this electrocardiographic pattern. A fatal outcome was usually the result of new and severe anginal attacks, followed by different electrocardiographic changes. It is likely that infarction which is indicated by the pattern $T_1 < T_3$ involves only the inner layers of the myocardium. It has been shown that injury of the epicardial portions invariably causes high

take-off of the S-T segment; this does not happen when the subendocardial layers of the heart muscle are injured.^{10, 11} Also, the appearance of a W-shaped QRS complex in Lead IV in eight of our cases points to involvement of the inner layers of the myocardium.¹²

The electrocardiographic pattern $T_1 < T_3$ occurs rather frequently. During the last two and a half years, we have observed it in thirty cases in which there was evidence of inadequate nutrition of the heart muscle. It is of great diagnostic value, especially when other electrocardiographic changes indicative of myocardial infarction are absent, as happened in nine of our cases. Case 7 affords a good illustration. Abnormally low voltage of T_1 is not an invariable feature of the pattern $T_1 < T_3$. The latter usually results both from flattening of T_1 and an increase in the voltage of T_3 . Occasionally, however, T_1 is of normal amplitude, and it is primarily the increase in voltage of T_3 which causes reversal of the ratio of voltage of T_1 and T_3 .

The pattern $T_1 < T_3$ is not specific of myocardial infarction. It may be found in the absence of heart disease when the heart is vertical, and in the presence of pulmonary emphysema. During the last two and a half years, we have observed this in five instances. Especially in cases in which there is a low R_1 , the pattern $T_1 < T_3$ should be evaluated cautiously, and a roentgenologic study of the chest be made in order to ascertain whether either of the above-named factors is responsible for the electrocardiographic changes. On the other hand, it should be remembered that myocardial infarction, by itself, may also cause a decrease in the amplitude of R_1 . When abnormal position of the heart and pulmonary emphysema have been ruled out, one should consider the possibility of myocardial infarction in older persons, especially in those who give a history of angina pectoris. In young patients, rheumatic heart disease is the most likely cause of the pattern $T_1 < T_3$. During the last two and a half years, we have observed this in five cases. The incidence of the pattern $T_1 < T_3$ in other diseases is almost negligible. During the interval mentioned above, we saw this pattern once with thyrotoxicosis, once in a case of severe anemia, twice with uremia, and in one instance with hypothyroidism.

Examples of the pattern $T_1 < T_3$ are readily available in the literature, especially in the current textbooks on electrocardiography. In Graybiel and White's "Electrocardiography in Practice"¹³ we found twelve examples of the pattern $T_1 < T_3$. In five cases (Figs. 103, 105, 121, 208, and 251) the clinical diagnosis was myocardial infarction. In four cases (Figs. 140, 221, 239, and 259) coronary heart disease was diagnosed. In one instance (Fig. 258), the diagnosis was acute and chronic rheumatic heart disease. In another case (Fig. 271) trichinosis was diagnosed. One tracing (Fig. 29), which also presented the pattern $T_1 < T_3$, was attributed to a healthy physician. He was 105 years old, and died one year after the tracing was taken.

In Katz' "Exercises in Electrocardiographic Interpretation"¹⁴ the pattern $T_1 < T_3$ is shown in eight tracings. Two of them (Cases 41 and 51) were from patients with rheumatic heart disease, and two others (Cases 70 and 79) were from patients with congenital heart lesions. In two instances (Cases 42 and 44) myocardial infarction was diagnosed. Of interest are Cases 3 and 63. In discussing Case 3, in which there were upright T waves in all leads, with the pattern $T_1 < T_3$, and with R_4 absent, the author remarked: "The patient, a male, aged 70 years, showed more than his expected disability from his arteriosclerotic heart disease clinically. . . . The record is surprisingly normal in view of the clinical history." In Case 63 there was, in the initial stage of posterior wall infarction, an increase in the amplitude of T_2 and T_3 , resulting in a reversed ratio of voltage of T_1 and T_3 ; later, inversion of T_2 and T_3 was observed. Thus, the pattern $T_1 < T_3$ may exceptionally develop during the acute stage of posterior wall infarction.

Katz' "Electrocardiography"¹¹ contains eighteen tracings with the pattern $T_1 < T_3$. In two instances (Fig. 76A and B) the heart was pendulous; in one case (Fig. 202A) there was pulmonary emphysema. In six cases (Figs. 110B, 128A, 132B, C, and D, 134B and C, 140B, and 143C and D) the diagnosis was myocardial infarction; in three cases (Figs. 175A and B, 180A, B, and C, and 195A) "progressive coronary insufficiency" was diagnosed. Other examples of the pattern $T_1 < T_3$ included two cases of rheumatic heart disease (Figs. 185B and 219B), two cases of vitamin deficiency (Figs. 210B and 211B, C, and D), and one case of hyperthyroidism (Fig. 205A). In two instances (Figs. 71B and 73B), the clinical data and the diagnosis were not reported.

In a paper, "Delayed Electrocardiographic Changes in Coronary Occlusion,"¹⁵ Strauss presented a case (No. 3) in which there were a flat T_1 and an elevated T_3 a day after a severe anginal attack (Chart 3C). The author remarked that the electrocardiographic changes were minimal, and "definitely out of line with the history and findings of a coronary occlusion."

In a paper by Feil¹⁶ we found two tracings (Case 8, Fig. 2b, and Case 15, Fig. 3b) which presented the pattern $T_1 < T_3$ during "preliminary pain in coronary thrombosis."

In a case reported by Wilson and Johnston,¹⁷ the pattern $T_1 < T_3$ (Case 2, Fig. 1C) occurred. The tracing was from a patient who suffered from angina pectoris and had attacks of pain even during rest; one severe attack was brought on by shoveling snow.

Bellet, Kershbaum, and Furst¹⁸ reported a case in which development of the pattern $T_1 < T_3$ was observed after shock treatment (Case 2B). Later, T_1 , T_2 , and T_4 became inverted, and leucocytosis developed. The authors thought that hemorrhage into the ventricular myocardium might have been responsible for the electrocardiographic changes.

CONCLUSIONS

Evidence derived from our own observations and from reports in the literature indicates that the electrocardiographic pattern $T_1 < T_3$ is, in the overwhelming majority of cases, equivalent to the T_1 type of myocardial infarction. This is especially true when the patient is over 40 years of age and gives a history of angina pectoris. In young persons, rheumatic heart disease is the more likely cause. The incidence of the pattern $T_1 < T_3$ in other diseases, such as thyrotoxicosis, uremia, congenital heart disease, vitamin deficiency, and trichinosis, is rare and almost negligible. A vertical position of the heart, in the absence of heart disease, and pulmonary emphysema may also occasionally cause reversal of the ratio of voltage of T_1 and T_3 .

SUMMARY

Forty-five cases, in which the electrocardiographic pattern $T_1 < T_3$ occurred in the absence of inversion of T , are reported. In 75 per cent of the cases, clinical and laboratory data furnished dependable evidence of the presence of recent or old myocardial infarction. In the remaining 25 per cent there were symptoms and signs suggestive of coronary arteriosclerosis and ischemic myocardial necrosis. Similar cases are cited from the reports of others.

Under normal conditions T_1 is of greater amplitude than T_3 . Reversal of the ratio of voltage is occasionally observed with a vertical position of the heart in the absence of heart disease, and with pulmonary emphysema. In the overwhelming majority of cases, the pattern $T_1 < T_3$ is equivalent to the T_1 pattern of myocardial infarction. It is also occasionally observed in rheumatic heart disease, and in rare cases of congenital heart lesions, thyrotoxicosis, anemia, vitamin deficiency, uremia, and trichinosis.

When the pattern $T_1 < T_3$ occurs in persons over 40 years of age who give a history of angina pectoris, myocardial infarction should be considered first in the diagnosis. The pattern $T_1 < T_3$ may indicate recent or, more often, old myocardial infarction. It is of particular value in the recognition of infarction when other electrocardiographic changes are absent and the tracing appears to be "within normal limits." In young persons, rheumatic heart disease is the most frequent condition underlying the pattern $T_1 < T_3$.

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THE EFFECTS OF VARIOUS SULFONAMIDE DRUGS ON THE ELECTROCARDIOGRAM OF THE DOG

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ALTHOUGH a great many papers have been published concerning the effects of various sulfonamide drugs on liver, central nervous system, kidney, etc., relatively few have dealt with the effect of these drugs on cardiac muscle.

Nelson¹ reports histopathologic changes in the cardiac muscle of rabbits and hens. In a group of twenty-one rabbits to which fatal doses of sulfanilamide had been given, fourteen hearts were examined. All sections were negative, and two on which fat stains were made were fat-free. In a second group of fifteen rabbits which received fatal doses of sulfanilyl sulfanilamide, twelve hearts were examined, and eleven of these were negative. In a group of seventeen hen hearts, however, twelve were negative, two were fat-free, and five showed myocardial damage. Hawkins,² reporting on the pharmacologic actions of sulfanilamide, states that it has almost no action on the heart of the frog. Litchfield,³ who also used sulfanilamide on frog hearts, reported no apparent effect on rate, amplitude, or type of contraction with concentrations below 300 mg. per cent. Using a much higher concentration (800 mg. per cent) on one heart, he found slowing in rate, decrease in amplitude, and rapid cessation of activity. Mendenhall and Shreeve,⁴ who also worked with the frog heart, reported that the effect of sulfanilamide (0.25 per cent solution) is stimulation followed by depression. The effect is progressively more depressive as the concentration of sulfanilamide is increased.

On the other hand, Barnes,⁵ who studied turtle hearts, reports "the excised auricles of the turtle are chronotropically and inotropically stimulated by 1 per cent sulfanilamide. The oxygen consumption of slices of ventricle of the turtle heart is not affected by 1 per cent sulfanilamide."

Dozzi⁶ reports one case of transient nodal rhythm and myocardial damage in man following the use of sulfanilamide. Scheinberg and Ingle⁷ also present evidence suggestive of myocardial damage in man. Each of these, however, is a report of a single case, and in one of them⁷ there was no record of an electrocardiogram previous to the administration of the drug.

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Recently, French and Weller,⁸ in an extensive pathologic study of 238 patients who had been given sulfonamide drugs, reported interstitial myocarditis in 126 cases. They found that a similar condition was produced in the hearts of mice and rats by daily intraperitoneal injections of neoprontosil, sulfanilamide, sodium sulfapyridine, and sodium sulfathiazole.

The present study was undertaken to show the effects of various sulfonamide drugs on the electrocardiogram of the dog. The series includes sixteen dogs. These animals were trained to lie perfectly still (unanesthetized) while the electrocardiogram was being taken. From nine to sixteen control tracings, over a period of two weeks, were taken on each animal before the drug experiments were begun.

All of the drugs were administered intraperitoneally. They were distributed as follows: sodium sulfapyridine, six dogs; sodium sulfathiazole, five dogs; and sodium sulfadiazine, five dogs. Of this group, each drug was used on one dog in a 28-hour experiment (discussed later). The other thirteen experiments were carried out in a series. Each series represented eight to seventeen daily doses, ranging from 0.15 Gm. to 0.2 Gm. per kilo of body weight. These were given on four to five successive days, and rest periods of one week were allowed between series.

During the 28-hour experiment, the concentration of the drug in the blood was ascertained by the method of Bratton and Marshall,⁹ using the photoelectric colorimeter. The concentrations attained gave the same toxic effects which have been repeatedly reported in both man and experimental animals, namely, loss of appetite, nausea, vomiting, and kidney involvement. These toxic effects were observed in each case in the weekly series, although blood levels were not routinely ascertained.

Six hundred forty-two tracings (Lead II) were analyzed. These were measured for heart rate and conduction time (P-R interval), and carefully checked for any abnormality of rhythm or conduction.

In several of the animals, an increase in heart rate, with a corresponding decrease in P-R interval, was observed in the tracings taken three to four hours after the administration of the drug. The rate and P-R interval had returned to normal within twenty-four hours. In two dogs, ventricular premature systoles were present in a few tracings. Also, in several dogs, T₂ was inverted. However, this inversion is rather common in dogs, and the form of the wave did not appear altered by the administration of the drug.

Aside from these changes, in no case was there any apparent myocardial damage due to the drug.

In order to reproduce as nearly as possible the conditions in acute infections in which the drug is given in a large initial dose, followed by smaller doses at three- or four-hour intervals, a 28-hour experiment was performed.

Four dogs were used—one control, and one each for sodium sulfapyridine, sodium sulfathiazole, and sodium sulfadiazine.

On each animal, control electrocardiograms (eight to sixteen in number) had been taken during the two weeks preceding the test. On the day of the experiment, at 2 P.M., an electrocardiogram was taken and

blood drawn from the jugular vein for blood sugar, pH, and drug concentration estimations. Drugs were injected immediately after this procedure in each case; 0.2 Gm. per kilo of body weight was the initial dose, followed by 0.1 Gm. per kilo at four-hour intervals, until a total of six doses had been given.

The results of these 28-hour experiments are shown in the tables. Control dog 1 was given sodium sulfadiazine (0.2 Gm. per kilo) daily from April 13 to 17—five doses in all. On April 25, eight days later, she was used as the control for the 28-hour experiment. As can be seen from Table I, there were still traces of sodium sulfadiazine in the blood.

TABLE I
DOG 1 CONTROL
(28-HOUR EXPERIMENT)

PROCEDURE	TIME	DRUG LEVELS IN BLOOD			B.L.S.	PH.	H.R.	P-R
		FREE	TOTAL	COMB.				
Control	2 P.M.	7.8	6.7	0	52	7.34	57	0.130
1	6 P.M.	--	--	--	47	7.30	77	0.120
2	10 P.M.	4.5	4.5	0	51	7.32	--	----
3	2 A.M.	4.1	3.8	0	37	7.28	84	0.116
4	6 A.M.	2.7	2.3	0	36	7.28	64	0.123
5	10 A.M.	2.7	2.4	0	54	7.33	76	0.124
6	2 P.M.	2.3	2.3	0	56	7.28	70	0.124
29 hours after drug had been discontinued							77	0.120

B.L.S.=Blood sugar (Somogyi-Schaffer)

H.R.=Heart rate

P-R=A-V conduction time in seconds

Table II shows the effect of the administration of sodium sulfapyridine. There was a marked increase in heart rate, with a corresponding decrease in P-R interval, as the drug concentration in the blood increased. Twenty-nine hours after the drug had been discontinued, the heart rate fell and the P-R interval increased correspondingly.

TABLE II
DOG 2 SODIUM SULFAPYRIDINE
(28-HOUR EXPERIMENT)

PROCEDURE	TIME	DRUG LEVELS IN BLOOD			B.L.S.	PH.	H.R.	P-R
		FREE	TOTAL	COMB.				
Control	2 P.M.	0.13	0.13	--	75	7.34	86	0.100
1	6 P.M.	21.5	20.5	0	84	7.23	136	0.104
2	10 P.M.	26.6	27.8	1.1	84	7.24	150	0.096
3	2 A.M.	32.4	32.4	0	126	7.22	139	0.096
4	6 A.M.	34.3	35.3	1.0	63	7.28	139	0.096
5	10 A.M.	37.7	38.5	.8	69	7.24	158	0.099
6	2 P.M.	40.3	41.4	1.1	72	7.24	176	0.096
29 hours after drug had been discontinued							77	0.124

Table III, which depicts the effects of the administration of sodium sulfadiazine, also shows an increase in heart rate, but not as marked as after sodium sulfapyridine. Table IV, which summarizes the sulfathiazole effects, also shows a marked increase in heart rate, with a cor-

TABLE III
DOG 3 SODIUM SULFADIAZINE
(28-HOUR EXPERIMENT)

PROCEDURE	TIME	DRUG LEVELS IN BLOOD			Bl.S.	pH.	H.R.	P-R
		FREE	TOTAL	COMB.				
Control	2 P.M.	0	0	0	55	7.30	65	0.116
1	6 P.M.	27.6	26.1	0	47	---	94	0.120
2	10 P.M.	36.0	38.5	2.5	44	7.29	90	0.124
3	2 A.M.	51.0	54.5	3.5	41	7.28	79	0.120
4	6 A.M.	62.8	69.0	6.2	37	7.27	83	0.118
5	10 A.M.	76.6	82.1	5.5	41	7.22	70	0.120
6	2 P.M.	87.6	96.5	6.9	45	7.21	74	0.124
48 hours after drug had been discontinued							86	0.110

TABLE IV
DOG 4 SODIUM SULFATHIAZOLE
(28-HOUR EXPERIMENT)

PROCEDURE	TIME	DRUG LEVELS IN BLOOD			Bl.S.	pH.	H.R.	P-R
		FREE	TOTAL	COMB.				
Control	2 P.M.	0	0	0	65	7.34	80	0.124
1	6 P.M.	12.1	12.2	0.1	57	7.35	86	0.124
2	10 P.M.	10.2	10.4	0.2	57	7.34	94	0.120
3	2 A.M.	12.3	13.8	1.5	72	7.32	109	0.116
4	6 A.M.	12.9	13.6	0.7	58	7.32	107	0.114
5	10 A.M.	11.0	11.1	0.1	59	7.32	92	0.124
6	2 P.M.	11.8	13.0	1.2	71	7.31	78	0.116
29 hours after drug had been discontinued							102	0.112

respondingly decreased P-R interval, as the drug concentration in the blood increased. Twenty-nine hours after the drug had been discontinued, the heart rate was still above the control. This increase had disappeared when a tracing was taken four days later.

All tracings obtained during the 28-hour experiment were carefully checked for abnormalities of rhythm and conduction. The results confirmed those obtained in the series experiments. In no case in this study was any myocardial damage found which could be attributed to the use of the drug.

Except for two dogs which died of distemper during the year, the others remained in apparently splendid physical condition.

SUMMARY

Experiments were performed on sixteen dogs to show the effects of various sulfonamide drugs. Sodium sulfapyridine, sodium sulfadiazine, and sodium sulfathiazole were used.

Six hundred forty-two tracings (Lead II) were taken, and measured for heart rate and P-R interval. All were carefully checked for abnormalities of rhythm or conduction.

No evidence of myocardial damage which could be attributed to the drug was found in this study.

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THE BASAL WEIGHT LEVEL IN THE TREATMENT OF CONGESTIVE HEART FAILURE

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THE foremost question in the mind of the physician when dealing with congestive heart failure is: "How can I attain and then maintain a completely edema-free state for my patient?" This, of course, is the goal toward which diuretic therapy should be meticulously directed. Previous reports^{1, 2} have emphasized the value of a graphic record of the daily weight of the patient in the treatment of congestive heart failure. Its advantages have been pointed out in those papers and will not be reviewed here.

It occurred to us, however, that an accurate daily weight record could provide the instrument by which the physician would be certain to know when his patient had attained the ideal state. As will be shown, it is possible to remove all of the edema from the extracellular tissue spaces by the intensive use of mercurial diuretics. This end result is designated as the "basal weight level." It should be pointed out that this term does not represent merely the disappearance of edema in the usual sense, but actually describes a state, as indicated by the weight chart, in which no additional fluid can be driven out of the body by the further use of diuretics.

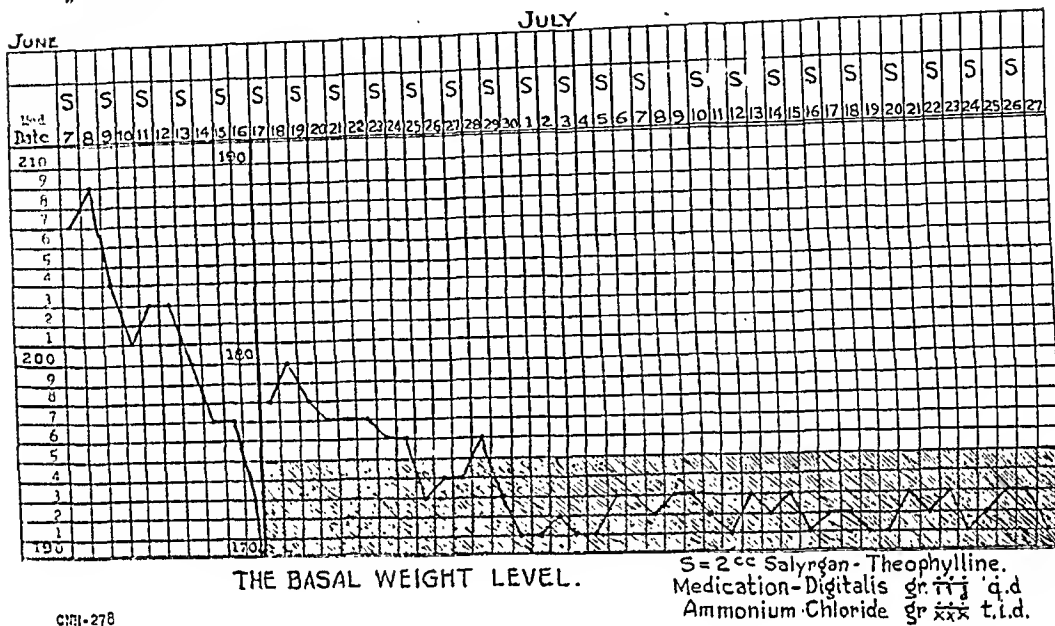
We present here a simplified procedure which has been used to bring about and maintain this "basal weight level" in seventeen patients who have been followed continuously for periods varying from 76 to 977 days (Table I).

At present, all except five, who have died, remain under our observation. Another woman, who recently developed congestive heart failure of hypertensive origin, was also treated in this way, and her weight chart is reproduced in Chart I. Although she is not included in the group of seventeen cases which were studied at greater length, her chart shows a characteristic type of response, and further signifies the ready applicability of this system of therapy.

The procedure which is used in these cases may be described as follows: The patient, in the usual hospital gown, is weighed daily, before breakfast, and the weight is recorded on the chart (Chart I). Fluids are not restricted. Digitalis is employed in the accepted dosage as the need arises in each case. Ammonium chloride is given in the usual dose of 90 grams (6 Gm.) daily. A mercurial diuretic is administered on alternate days. It is preferred that 2 c.c., together with

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an equal amount of 1 to 2 per cent procaine hydrochloride solution, be given intramuscularly into the buttock in the morning (preceded at the outset by a test dose of 0.5 c.c.).* Usually a more or less rapid weight loss results, as can be seen on the chart (Chart I), until a plateau develops in the curve. From that point, the height of the curve remains unchanged, although the mercurials continue to be injected on alternate days as before.



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Chart I.

It is arbitrarily considered that the "basal weight level" has been reached when the daily weight changes do not exceed a 5-pound range for a period of fourteen consecutive days. (This area can be conveniently shaded in colored crayon.) At this juncture the mercurial is discontinued until further need for it is indicated on the chart by any rise in the weight above the "basal weight level." The frequency with which the mercurial injections are required seems to be somewhat proportional to the severity of the underlying heart disease. For example, in some cases the injection must be given as often as every other day for an indefinite period in order to maintain the patient at his "basal weight level," whereas, in others, the patient's weight is so constant that it may be represented by a straight line. It has been the policy in the latter group to utilize a so-called "trial dose" in order to avoid an undesirable accumulation of fluid.

*In "A Review of the Toxic Manifestations of Mercurial Diuretics in Man," DeGraff and Nadler comment that "in the reported cases of sudden death from mercurial injection no deaths have been reported from the administration of the mercurial diuretics intramuscularly or by rectum." The intramuscular administration of the mercurials has been used exclusively in our series, without any untoward reactions. Furthermore, the diuresis after such injections is quite satisfactory, and probably more prolonged than when the intravenous method is employed.

TABLE I
OBSERVATIONS DURING FREQUENT ADMINISTRATION OF MERCURIALS

PATIENT	DURATION OF TREAT- MENT	MERCURIALS	ADMISSION URINE			PRESENT URINE			R.B.C.	AUTOPSY
			ALB.	W.B.C.	CASTS	ALB.	W.B.C.	CASTS		
1. D. S. (D.)	155 days	48 injections	0	0	0	0	0	0	0	No tubular damage
2. P. M. (D.)	321 days	90 injections	3+	0	0	2+	0	0	0	Severe cloudy swelling
3. M. B. (D.) (F.)	78 days	32 injections	2+	0	0	4+	few	0	0	No tubular damage
4. J. G. (D.)	158 days	28 injections	0	0	0	0	0	0	0	No autopsy
5. J. M. (D.)	424 days	41 injections	0	0	0	0	0	0	0	No tubular damage
6. W. D.	555 days	131 injections	0	0	0	0	0	0	0	No tubular damage
7. F. F. (F.)	977 days	214 injections	3+	0	0	0	0	0	0	No tubular damage
8. L. M.	397 days	107 injections	1+	0	0	0	0	0	0	No tubular damage
9. J. N.	418 days	11 injections	4+	0	0	0	0	0	0	No tubular damage
10. M. R. (F.)	480 days	129 injections	0	0	0	0	0	0	0	No tubular damage
11. F. S.	340 days	22 injections	0	0	0	0	0	0	0	No tubular damage
12. B. S.	584 days	73 injections	0	0	0	0	0	0	0	No tubular damage
13. A. S.	412 days	49 injections	0	0	0	0	0	0	0	No tubular damage
14. H. S.	294 days	67 injections	0	0	0	0	0	0	0	No tubular damage
15. R. M. (F.)	659 days	212 injections	0	0	0	0	0	0	0	No tubular damage
16. J. D.	76 days	32 injections	0	0	0	0	0	0	0	No tubular damage
17. J. P.	381 days	102 injections	4+	0	0	2+	0	0	0	No tubular damage
Total	6,709 days	1,388 injections	2+	0	0	0	0	0	0	No tubular damage
Average	394.65 days	81.64 injections	0	0	0	0	0	0	0	No tubular damage
(D.) = Deceased										
(F.) = Female										
		occ. = Occasional								
		HPF = High-Power Field								
		hyal. = Hyaline								
		gran. = Granular								

It is to be emphasized that approximately 10 pounds of fluid can accumulate in the body before even minimal traces of edema, e.g., pretibial edema, can be demonstrated clinically, but the present method detects and eliminates this undesirable accumulation of latent fluid well within the 5-pound limit of the "basal weight level" (see Chart I). It is unnecessary to wait for the reappearance of gross edema as an indication for the next mercurial injection, and, therefore, edema as such does not exist under this regime. Any system of therapy which embraces diuretics in the management of congestive cardiac failure and employs the clinical detection of edema as a guide must take into account the continuous presence of latent fluid in the tissues. On the other hand, the patient at the "basal weight level" is maintained at all times in an edema-free state.

It is to be noted that this method employs at the outset a more frequent rate of administration than is customary with the intravenous route, but we feel that this is the very reason for its success, because a more *continuous* diuresis is established.

We have been keenly aware of the possibility that various untoward effects might result from such an intensive use of mercurials. Usually, renal and gastrointestinal disturbances are the reactions which are associated with the use of mercury in toxic doses.

DeGraff and Nadler,³ in describing changes produced in the kidney by mercurial diuretics, emphasize the degeneration of the tubular epithelium. They state that the abnormalities in the urine produced by irritation from mercurial diuretics appear in the following order: (1) casts, (2) albumin, (3) leucocytes, and (4) erythrocytes. Several instances of mild renal irritation from mercurials have been reported by Sprague and Graybiel,⁴ Herrmann and Decherd,⁵ Klinghoffer,⁶ Brown and Englebach,⁷ and others. In a series of thirty autopsies on patients who received salyrgan during life, Tarr and Jacobson⁸ found only one patient with a renal lesion suggestive of mercurial intoxication. In our series of five deaths (Table I, Patients 1 to 5), four autopsies were performed. No indication of tubular damage was found in any case, although in one there was evidence of cloudy swelling of the kidneys. We have focused our attention on the urine in every case, and reference to Table I reveals that, over a long period of observation, during which as many as 200 or more injections were given, urinalysis in most cases actually showed a striking improvement, rather than the development of renal damage. This improvement is more than likely due to the disappearance of the passive congestion in the kidneys. No gastrointestinal symptoms, such as stomatitis, salivation, and hemorrhagic colitis, occurred in our series.

In general, we are in agreement with Wiseman,⁹ Maxwell, Scott, and Harvey,¹⁰ Dixson,¹¹ Levine,¹² and Fineberg¹³ on the low toxicity of the mercurial diuretics. Hence, with our method, there has been no cause

to fear even the most frequent use of mercurials that is necessary to bring patients with severe congestive cardiac failure to the "basal weight level."

SUMMARY

1. In a series of seventeen cases of congestive heart failure which were followed over varying periods of time (76 to 977 days), we produced and maintained a completely edema-free state which we have termed the "basal weight level."
2. The simple procedure which is employed in gaining this end is described and exemplified by the actual weight chart in a typical case.
3. The advantages of a system whereby the cardiac patient is at all times assured of freedom from edema are emphasized.
4. No untoward reactions attributable to the frequent use of the mercurials were noted with this method, either in the urine or at post-mortem examination.

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BICUSPID AORTIC VALVES AND BACTERIAL ENDOCARDITIS

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CONGENITAL cardiac defects, especially a bicuspid aortic valve, have generally been assigned an important role in the pathogenesis of bacterial endocarditis.¹⁻⁵ Such defects are considered to be susceptible to the development of endocarditis.

Among fifty adult hearts with bicuspid aortic valves, there were eight with superimposed bacterial endocarditis. Analysis was undertaken to ascertain the relation of the bicuspid lesions to the bacterial disease. The results do not support the view that a congenitally bicuspid aortic valve is a significant precursor of bacterial endocarditis.

MATERIALS AND METHODS

The material consisted of eight adult hearts, all with a bicuspid aortic valve which was the seat of bacterial endocarditis. The hearts were studied grossly and microscopically to ascertain (1) the type of bicuspid aortic valve, (2) the nature and distribution of the bacterial disease, and (3) whether or not there were stigmas of rheumatic fever.

The type of bicuspid lesion was established by study of the raphe, or ridge, behind the conjoined aortic cusp. The gross appearance of each raphe was noted, and then transverse or longitudinal microscopic sections were obtained. Serial sections were made in several instances. The preparations were stained with hematoxylin and eosin, Weigert's method for elastic tissue, or the combined Weigert and Van Gieson methods for elastic and fibrous tissue.

The bacterial lesions were subdivided into acute bacterial endocarditis and endocarditis lenta (subacute bacterial), depending on their gross and microscopic character. An important morphologic criterion of endocarditis lenta is the presence of organization tissue at the base of the vegetations. The valvular distribution of the lesions was noted in each heart.

To detect rheumatic stigmas, the hearts were subjected to microscopic study of blocks made according to the method of Gross, Antopol, and Sachs,⁶ and numerous additional sections were made from the valves.

Only unequivocal stigmas of rheumatic heart disease were accepted. Grossly, such stigmas include thickening, shortening, and commissural fusion of the valves, especially the mitral and tricuspid, thickening and adhesion of the chordae tendineae, nodular thickening and wrinkling of the left atrial endocardium, and fibrous pericardial adhesions. Characteristic microscopic lesions consist of vascularity, exudate, and fibrosis in the attachment and free portion of the valves, involving especially the auricularis layer of the mitral and tricuspid valves and the ventricularis layer of the semilunar valves, vascularity and reduplication of the elastica of the endocardium of the left atrium and the subaortic angle, and Aschoff nodules in the myocardium.

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RESULTS

Type of Bicuspid Aortic Valve.—Seven of the bicuspid aortic valves were acquired and one was congenital.

Of the seven acquired lesions, the raphe was situated at commissure A* in six, and at commissure B in one. Grossly, the raphes were all similar in appearance. Each consisted of a firm ridge of fibrous tissue, usually wider distally than proximally, and passing obliquely in the sinus of Valsalva from the proximal origin at the upper commissural level to insert distally into the conjoined cusp. The insertion was in the basal third of the conjoined cusp in all but one instance, in which it was located in the outer third. The raphes were symmetrical in six cases, and slightly irregular or distorted in two cases because of calcific deposit. None of the lesions revealed a fissure in the outer surface.

Microscopically, the raphes were composed of dense, hyalinized, fibrous tissue and contained little or no elastica. In longitudinal sections, vascularity and sometimes exudate were present in the ventricular layer along the base of the raphe, especially in the distal segment, and were usually prominent in the region of attachment of the valve and the subaortic angle. In transverse sections, vessels were seen in the lateral or basal regions, corresponding to the attachment of the fused cusps. In every case the junction of aortic media and annulus fibrosus occurred behind the proximal extremity of the raphe, and the annulus was situated anterior to the media.†

In the congenitally bicuspid aortic valve, the ridge was situated at commissure A. It consisted grossly of a long, narrow, hemicylindric elevation of aorta, of uniform width and depth, projecting only slightly into the sinus of Valsalva, and directed in the long axis of the aorta. In the distal half, the surface revealed a longitudinal fissure. Microscopically, the ridge was composed almost entirely of elastic tissue, whorled centrally, and continuous laterally with that of the aortic media. The elastica terminated in the distal part of the ridge by overlapping the annulus fibrosus both anteriorly and posteriorly; the posterior overlap descended to a lower level than the anterior. No inflammatory changes were observed in the ridge.

Lesions of Bacterial Endocarditis.—All eight bicuspid aortic valves were the seat of superimposed bacterial endocarditis. The lesions were acute bacterial in four cases and endocarditis lenta in four cases. The gross and microscopic appearance of the vegetations was characteristic. In six cases the bacterial disease was confined to the aortic valve, whereas in two others, in both of which the bicuspid aortic valve was acquired, the mitral leaflets also showed vegetations.

*The following nomenclature of the aortic valve is used: the aortic cusps are designated according to the situation of the coronary ostia, as the left, the right, and the noncoronary cusps.
The left-right commissure is referred to as commissure A, the right-noncoronary commissure as commissure B, and the left-noncoronary commissure as commissure C.
†When the annulus is anterior to (or in front of) the aortic wedge, it is separated by the latter from the pericardium. If the annulus be posterior to (or behind) the wedge, it is in contact with the pericardium.

Lesions of Rheumatic Fever.—In every case, including the congenital bicuspid lesion, the aortic valve showed gross changes indicative of rheumatic disease. The cusps were the seat of slight to marked thickening, especially along the line of closure. In the conjoined cusps, thickening was generally prominent in the region bordering on the commissural raphe. Calcific nodules were present in slight or moderate amount in five cases, either in the substance of the cusps or projecting into the sinuses of Valsalva. Inrolling of the free margins was observed in two instances. In only one case, that of an acquired bicuspid aortic valve, with the raphe at the commissure A, was there additional commissural fusion, namely, a submarginal adhesion at commissure B.

Microscopically, the aortic cusps generally showed lesions characteristic of rheumatic fever, such as fibrosis, vascularity of the attachment and free portion, and calcific deposit.

Gross rheumatic stigmas other than those of the aortic valve were observed in six of the eight hearts. Chronic, nondeforming mitral valvulitis was present in six cases, nondeforming tricuspid valvulitis in two instances, nodular thickening of the left atrium in two instances, and pericardial adhesions in one case. In two hearts with acquired bicuspid aortic valves which were the seat of acute bacterial endocarditis, no conclusive, gross, rheumatic stigmas were found outside the aortic valve. In the heart with a congenitally bicuspid aortic valve, there was a nondeforming rheumatic lesion of the mitral valve.

Seven of the eight hearts revealed definite microscopic evidence of rheumatic disease in situations other than the aortic valve. There were lesions of the mitral valve in seven cases, of the left atrium in three cases, and the tricuspid valve in three instances. Aschoff nodules were seen in the left ventricle in one case. In one of the two hearts which showed isolated rheumatic aortic valvulitis in the gross, the microscopic stigmas of rheumatic fever were also limited to the aortic valve. In the heart with a congenitally bicuspid aortic valve, rheumatic stigmas were present in the mitral valve and left atrium.

COMMENT

Early writers on the subject of bicuspid aortic valve did not distinguish clearly between congenital and acquired types.⁷⁻⁹ Although the possibility of acquired origin was admitted, it was generally thought that most of the lesions were congenital. Osler⁹ held this view on the basis of gross criteria which are now known to be inadequate.^{10, 11} The frequent association of a bicuspid aortic valve with bacterial endocarditis was attributed to the assumption that the congenitally defective tissue is susceptible to bacterial invasion.

Lewis and Grant¹ were the first to distinguish morphologically between congenital and acquired bicuspid aortic valves. They directed their attention especially to the congenital ridge behind the conjoined cusp. This was studied in its entirety with serial transverse micro-

scopic sections stained for elastic tissue. It was found to consist chiefly of elastic lamellae which were derived from the adjacent aorta and passed across the ridge in symmetrical manner. In the central portion there was a peculiar whorling pattern. In addition, the elastica extended down almost to the distal end of the ridge, and its terminal portion was frequently anterior to the annulus fibrosus.

In contrast, the ridge, or raphe, behind the conjoined cusp of the aortic valve revealed a structure derived from that of two fused cusps. Residua of chronic inflammation could be observed. The raphe contained no elastica. The junction of aortic media and annulus fibrosus occurred in the proximal extremity of the raphe, and the usual commissural relation was maintained, namely, the annulus was superficial to the elastica.

Lewis and Grant's material comprised a total of thirteen congenitally bicuspid aortic valves. Of these, eight occurred among a group of thirty-one consecutive adult hearts with endocarditis lenta. Thus, the authors stressed not only the frequency of a congenitally bicuspid aortic valve, but also its importance as a predisposing cause of bacterial endocarditis. The latter was explained by the theory that the congenital deformity constitutes a focus which is favorable for the implantation of bacteria. The authors estimated that 23 per cent of all persons with congenitally bicuspid aortic valves would develop endocarditis lenta after reaching adult life.

The validity of Lewis and Grant's work, especially with respect to the specific morphology of the congenital ridge, was later questioned by Gross.¹⁰ Such supposedly congenital characteristics as whorling and continuity of the elastica, and alteration of the terminal aortic wedge insertion into the annulus fibrosus, were attributed by him to an inflammatory origin. Gross maintained that practically all bicuspid aortic valves in adults are acquired lesions, and are produced in most instances by rheumatic fever. This etiological factor readily explained their frequent association with superimposed bacterial disease.

Recently, Koletsky¹¹ studied the morphology of bicuspid aortic valves in newborn babies and infants. Here the lesions were undoubtedly congenital in origin. The microscopic structure of the congenital ridge was studied by means of serial transverse and longitudinal sections. Thus, an adequate means was provided for ascertaining the nature of bicuspid aortic valves in adults. In the latter, the distinction between congenital and acquired lesions was found to depend solely on structural differences between the congenital ridge and the acquired commissural raphe.^{11, 12}

The gross appearance of the congenital ridge is characteristic. It consists of a long, narrow, barlike elevation of the aorta, symmetrical, of uniform width and depth, and directed in the long axis of the aorta. The microscopic appearance is similar to that described by Lewis and Grant, except for the junction of aortic media and annulus fibrosus in

the distal part of the ridge. This junction generally occurs in an inverted V-shaped manner, with the aortic wedge overlapping the annulus both anteriorly and posteriorly, and with the posterior overlap usually descending to a lower level than the anterior. Occasionally the junction is beveled, and the elastic wedge is either entirely anterior or posterior to the annulus.

The raphe of acquired bicuspid aortic valves consists of a firm oblique ridge of connective tissue, usually wider distally than proximally, often symmetrical, but sometimes irregular or distorted, especially when calcific deposit is present. Occasionally the raphe is markedly depressed, and occupies a horizontal position at the bottom of the sinus of Valsalva.¹³ The microscopic structure is distinctive. The raphe is composed of dense hyalinized fibrous tissue, may or may not show calcific deposit, and has practically no elastica. Vascularity and exudate are observed, especially in the distal and basal portions. The junction between annulus fibrosus and aortic media occurs at the proximal origin of the raphe, where the media terminates posterior to the annulus.

The original review of protocol records at the Institute of Pathology revealed only eight acquired bicuspid aortic valves in 3,500 consecutive autopsies.¹² Since then, further experience has shown that the acquired lesion is much more common than this figure would indicate. Moreover, in adults it is considerably more frequent than the congenitally bicuspid valve. For example, in approximately the last three years there have been twelve acquired lesions in adults, as compared to one adult congenital lesion in 1,200 consecutive autopsies. In the past, instances of bicuspid aortic valve were undoubtedly overlooked.

Our present figures on bicuspid aortic valves are as follows. A total of fifty bicuspid aortic valves in adults, collected from the autopsy material of University Hospitals and several other Cleveland Hospitals, have been studied. The lesions were divided into acquired and congenital types, according to the criteria enumerated. Forty of the bicuspid aortic valves were acquired and ten were congenital. Of the latter, five were of simple type, i.e., with two normal cusps and no congenital ridge, whereas five revealed a conjoined cusp subdivided by a congenital ridge.

Thus, the great majority of bicuspid aortic valves in adults, in our experience so far, are acquired; a small number are congenital in origin. The former conclusion coincides rather closely with the observations of Gross. His suggestions, however, that congenitally bicuspid aortic valves are confined to children, and that the criteria for their recognition are invalid, are not acceptable. Gross's study was probably handicapped by absence in his material of examples of congenitally bicuspid aortic valves in infants or children. Possibly, however, no congenital lesions were present among the sixteen adult bicuspid aortic valves which he described.

To support the view that congenitally bicuspid aortic valves did not occur in adults, Gross pointed out that, in the adult, bicuspid aortic valves differ from those of children in whom the lesion is definitely congenital. For example, the aortic cusps are thin and delicate in children and thickened in the adult lesion. Moreover, other cardiac anomalies generally accompany the bicuspid valve in children and are absent in adults.

These arguments are valid only in a general way. Isolated congenitally bicuspid aortic valves have been observed in infants, as well as adult lesions both with and without other anomalies. Absence of other anomalies does not preclude a congenital origin for a bicuspid aortic valve, any more than their presence necessarily indicates that the bicuspid valve is congenital. Thus, a heart with a congenital deformity may be the seat of superimposed rheumatic disease, with acquired bicuspid aortic valve. Moreover, our study includes instances of congenitally bicuspid aortic valves with thick cusps in infants, and adult lesions with delicate cusps.

Lewis and Grant's view regarding the high incidence of a congenitally bicuspid aortic valve among patients with bacterial endocarditis has not been confirmed up to the present time. Their experience in this matter is contrary to ours. The difference is puzzling in view of the fact that Lewis and Grant used valid microscopic criteria to identify the congenital lesion. A critical review of their material, however, indicates that in a few cases the morphologic requirements for the congenital ridge appear not to have been adequately fulfilled, and that in a few others the interpretation is open to question. Thus, it is possible that some lesions designated as congenital were actually acquired.

Gross thought that most acquired bicuspid aortic valves are due to rheumatic fever, and a small number to degenerative lesions, such as Mönckeberg's sclerosis. Our studies, including those of Karsner and Koletsky,¹⁴ indicate that the lesions are solely inflammatory, and, in all probability, are produced by rheumatic disease. The evidence in favor of a rheumatic etiology is reasonably conclusive. The raphes of the conjoined cusps differ in no appreciable way, grossly or microscopically, from the commissural raphes of rheumatic aortic valves without bicuspid deformity. The pathologic changes in the aortic cusps, with respect to fibrosis, vascularity, calcific deposit, and elastic reduplications are morphologically indistinguishable from those which occur in rheumatic fever. Moreover, hearts with acquired bicuspid aortic valves generally show conclusive stigmas of rheumatic disease in regions other than the aortic valve. These stigmas are of both gross and microscopic nature, may be distributed focally or widely in the heart, and are most frequent in the mitral and tricuspid valves. Some data are available in the literature to indicate the frequency of bicuspid aortic valves at autopsy in cases of bacterial endocarditis.

On the basis of Lewis and Grant's work, the authors generally assume, without morphologic study, that the bicuspid lesions are congenital. Starling¹⁵ found four bicuspid aortic valves among thirteen cases of endocarditis lenta. Thayer¹⁶ reported three bicuspid lesions among twenty hearts with acute streptococcal bacterial endocarditis involving the aortic valve, although there were no such lesions in twenty-six similar cases of subacute type. Fulton and Levine¹⁷ observed two bicuspid aortic valves among thirty hearts with subacute bacterial endocarditis. In twenty-eight cases of subacute bacterial endocarditis in patients over 40 years of age, Bayles and Lewis¹⁸ found three bicuspid aortic valves (11 per cent). Braunstein and Townsend¹⁹ reported seven bicuspid lesions among fifty-eight cases of bacterial endocarditis; that they regarded the lesions as congenital is not stated.

Such data indicate that bicuspid aortic valves form a distinct type of underlying valvular defect in bacterial endocarditis. The lesion occurs in 6 to 12 per cent of cases of bacterial endocarditis. No adequate distinction between acquired and congenital lesions has been made, however, and no information offered regarding the presence of rheumatic fever, so that the importance of each type of bicuspid aortic valve in relation to the bacterial disease cannot be ascertained. That all the bicuspid lesions were congenital is doubtful.

The present study lends no support to the view that a congenitally bicuspid aortic valve is a significant precursor of bacterial endocarditis. It indicates that most bicuspid aortic valves in adults are acquired, and, in this respect, confirms the observations of Gross. Congenitally bicuspid aortic valves in infants and children are apparently not susceptible to bacterial disease. Of fourteen such lesions studied by the author, none showed superimposed bacterial endocarditis. The rheumatic nature of acquired bicuspid aortic valves readily explains the frequency of superimposed bacterial infection. In general, no congenital valvular defect can be considered as having led to the development of bacterial endocarditis until the presence of rheumatic disease has been excluded.

Consideration was given to the possibility that the bicuspid lesion, per se, apart from, or in addition to, the underlying rheumatic disease, might predispose to bacterial endocarditis. This was suggested by the fact that, in six of the eight cases, the bacterial disease was confined to the aortic valve. The problem was approached statistically. There were seven cases of bacterial endocarditis among forty acquired bicuspid aortic valves, an incidence of 17 per cent. In comparison, the general incidence of bacterial disease among rheumatic hearts was 12 per cent, i.e., 60 cases among 475 rheumatic hearts. However, among 100 unselected rheumatic aortic valves, with deformity comparable to the bicuspid lesion, there were fourteen cases of bacterial endocarditis

(14 per cent). The differences between these figures are too small to offer any clear-cut indication that the bicuspid deformity itself pre-disposes to bacterial disease.

SUMMARY AND CONCLUSIONS

Eight hearts with bicuspid aortic valves and superimposed bacterial endocarditis are described. The bacterial disease was acute in four cases and subacute in four cases. Seven of the bicuspid lesions were acquired, and one was congenital. Every heart showed definite stigmas of rheumatic fever. It is concluded that the bacterial lesions in each case were engrafted on the rheumatic disease.

Most bicuspid aortic valves in adults are acquired lesions produced by rheumatic fever. The latter, rather than the bicuspid state, pre-disposes these valves to the development of superimposed bacterial endocarditis.

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A TILTING BALLISTOCARDIOGRAPH

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IN ORDER to facilitate the use of the ballistocardiograph¹ in any position, it was desired to incorporate one within a tilting table. Such an arrangement would allow ballistocardiograms to be made immediately after changes in position, requiring a minimum of effort and cooperation on the part of the subject.

The chief difficulty encountered was the arrangement of a system for recording the motion of the ballistocardiograph in any position. This was overcome by means of a flexible lead tube attached to a Hamilton optical manometer. An additional advantage of this method was found to be the ease with which the ballistocardiogram could be recorded simultaneously on the same moving film with other physiologic measurements.

DESCRIPTION OF THE APPARATUS (FIG. 1)

A light (22 pound), but rigid, bed was constructed,* using $\frac{1}{2}$ inch 5-ply wood for the top, $\frac{1}{2}$ inch board for longitudinal trusses, and cast aluminum brackets for the end supports. To the latter, at the four corners of the bed, were bolted the spring clamps which held vertical flat springs of tempered tool steel, $\frac{1}{16}$ by $\frac{1}{2}$ inch by 3 inches. The upper ends of these four springs, in turn, were held in spring clamps bolted to the frame (4 inch channel) of the tilting table. The axle of the tilting table rested in bronze bearings upon the supporting frame, which was so constructed as to allow a tilt of 75° in either direction. Into one end of the axle a hole was drilled and tapped to take the fitting of the lead tube of the Hamilton manometer. The hole was extended 6 inches into the axle, then around a right angle turn to emerge from the axle under the bed. This opening was tapped to fit a compressible copper bellows, the other end of which was fixed to a crossbar running between the middle and outside wood trusses. Thus, any motion of the bed in relation to the axle caused a compression or extension of the bellows. The free stem of the bellows was drilled and tapped to take a needle valve, which allowed the bellows, the hole in the axle, the lead tubing, and the Hamilton manometer to be filled completely with a noncorrosive fluid† from a reservoir attached by rubber tubing to the side cock of the Hamilton manometer. The Hamilton manometer was then placed in an optical beam for recording.

When not in use, the ballistocardiograph bed was fixed in place within the tilting table frame by a screw at the end of the frame. The side cock on the Hamilton manometer was always left open to the reservoir until a record was ready to be made. This avoided undue motion and strain of the diaphragm in the head of the manometer.

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*By C. E. Clarke & Company, 1934 Revere Beach Parkway, Everett, Mass.

†Dupont "Zerex."

When the tilting table was set in any desired position, indicated by a graduated scale attached to the frame at the end of the axle, it could be rigidly clamped in that position by screwing tight the lock lever at the side of the frame. Then the fixing screw at the end of the frame was released to allow the ballistocardiograph bed to move. The side cock on the Hamilton manometer was closed, and the apparatus was ready to record the motions of the ballistocardiograph imparted to the bellows and, thence, to the Hamilton manometer.

Below:- Section of spring assembly, side view.

Right:- Section of bellows assembly, top view.

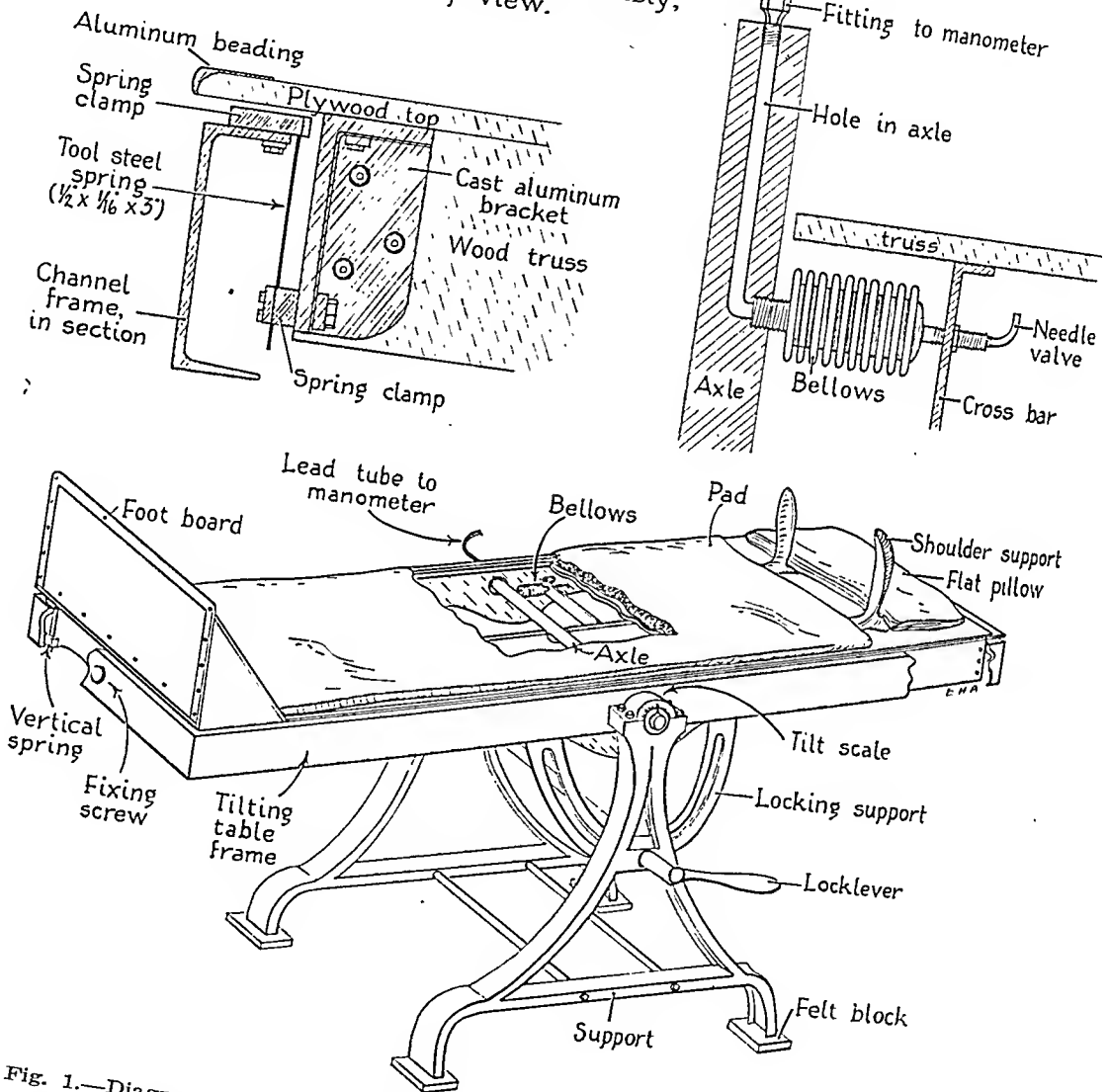


Fig. 1.—Diagram of the tilting ballistocardiograph. For description, see text.

Before changing the position of the table, the side cock to the Hamilton manometer was opened. Opening this cock to the reservoir brought the recording beam to rest at its base line. The bed was equipped with a footboard, and with adjustable shoulder supports to keep the subject from sliding when tilted. The machine was calibrated in any position by loading the bed with sandbags of about the same weight as the subject, and exerting a 500-gram pull on it in either

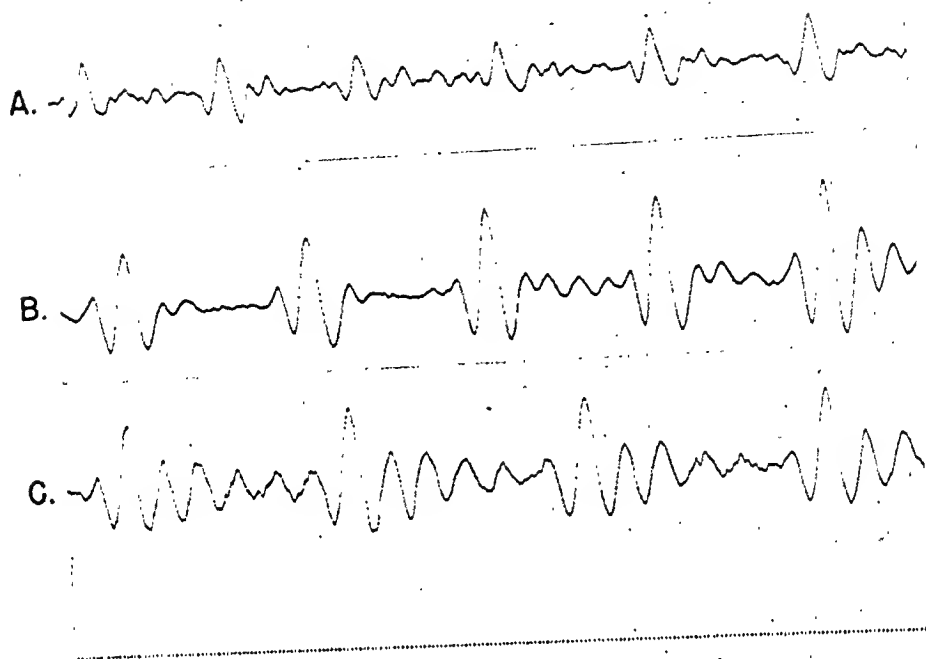


FIG. 2.—Normal ballistocardiograms in different positions. A, Upright 75°; B, horizontal; C, head down 20°.

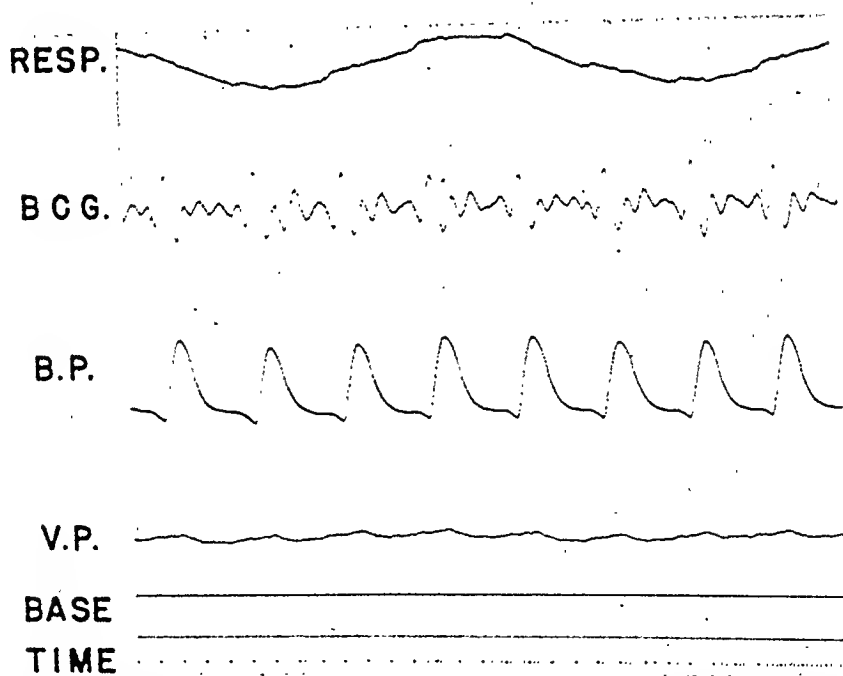


FIG. 3.—Optical record of respiration (inspiration down), ballistocardiogram (horizontal position), arterial pressure (Hamilton method), and venous pressure (Hamilton method) in a normal subject.

longitudinal direction. This was done by suspending a 500-gram weight across a pulley by a thread leading longitudinally to a pin set in the middle truss of the bed.

RESULTS

Fig. 2 shows typical ballistocardiograms taken in three different positions. Records in the horizontal positions have been uniformly satisfactory, but in the steeply tilted positions have often been confused by muscular tremors of the subject. Fig. 3 shows a number of different physiologic measurements recorded simultaneously with the ballistocardiogram. The apparatus has proved most useful in detecting quick or fleeting changes in cardiac function after alterations in position or other experimental conditions. It should also facilitate the study of patients with orthopnea, shock, or other abnormalities which demand a certain position.

SUMMARY

A ballistocardiograph was combined with a tilting table to allow ballistocardiograms to be made readily in any position of the subject.

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COMPARISON OF THE VALUE OF THE WELTMANN REACTION AND THE ERYTHROCYTE SEDIMENTATION RATE IN PATIENTS WITH RHEUMATIC HEART DISEASE

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THIS report is concerned with an analysis of the Weltmann serum coagulation test in a group of patients who had recently had rheumatic fever, and a comparison of the value of this test with the erythrocyte sedimentation rate. We were particularly interested in the problem of whether the development of rheumatic valvular lesions is related to the severity of the original attack of acute rheumatic fever, or to subsequent recurrences of rheumatic activity which are not easily detected by ordinary methods, i.e., "subclinical rheumatic activity." It was thought that variations in the coagulation band, as ascertained by the Weltmann reaction, might occur during periods of occult rheumatic activity, and that it would be informative to evaluate the usefulness of this test in such a group of patients.

The clinical course of rheumatic fever in eighty patients has been carefully observed during the past two years in an attempt to follow the gradual development of valvular heart disease. The patients were seen in the Cardiac Clinic and on the wards of The Johns Hopkins Hospital. Sixty patients had had acute rheumatic fever one or more times during the four years preceding this study. Signs of early mitral stenosis and insufficiency were present in seventeen, and twenty-five patients had marked rheumatic valvular lesions with cardiac enlargement. There were three patients with subacute bacterial endocarditis, one of whom died during the period of observations, and two of whom had apparently recovered after sulfonamide therapy just before they came into this group. Thirty-six patients had no signs of rheumatic heart disease and were under observation since their last attacks of acute rheumatic fever.

The patients were ambulatory, except for two patients during attacks of acute rheumatic fever and polyarthritis, and for some of the others during occasional nonrheumatic illnesses. The ages of the patients ranged from 8 to 40 years, with the greatest frequency around 18 to 20 and 35 years of age. They were seen at regular intervals during the period of study, and were carefully questioned and examined at each visit. Among the routine laboratory tests which were done at each visit were the following: leucocyte count, hemoglobin.

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estimation, throat culture, sedimentation rate, and Weltmann serum coagulation reaction. Electrocardiograms, stethograms, and other procedures were carried out as indicated.

The serum coagulation test, devised by Weltmann in 1930,¹ was an outgrowth of the observation that the coagulation temperature of human blood serum varies in different diseases, and that this coagulability is affected by the addition of electrolytes before heating. Less electrolyte was required in the presence of cirrhosis of the liver and chronic proliferative diseases than in the presence of acute infections such as lobar pneumonia. By varying the amounts of electrolyte added to the blood serum before heating, Weltmann developed the test which now bears his name.

METHOD

One-tenth cubic centimeter of unhemolyzed blood serum is added to each of ten test tubes containing 5 c.c. of varying concentrations of CaCl_2 arranged as shown in Table I.

TABLE I

TUBE NO.	1	2	3	4	5	6	7	8	9	10
CONC. OF CaCl_2 , PER CENT	0.10	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01

These tubes are then heated in boiling water for fifteen minutes, after which the test is read. The number of tubes in which evident flocculation occurs, rather than mere turbidity, is known as the coagulation band (C.B.). Coagulation occurs more readily in the tubes containing higher concentrations of electrolyte, normally in the first six or seven tubes (C.B. = 6, C.B. = 7). Coagulation in less than six tubes is known as a shift to the left, or a shortening of the coagulation band. Coagulation in more than seven tubes is known as a shift to the right, or a lengthening of the coagulation band.

A coagulation band of 6 or 7 has been found to be remarkably constant for normal sera. In exudative conditions, such as lobar pneumonia, there is a shift to the left, and in proliferative conditions, such as chronic fibrotic tuberculosis, there is a shift to the right. In marked congestive heart failure and in cirrhosis of the liver there is a shift to the right. There are characteristic changes in other conditions, such as parenchymatous liver disease.² The test has been used in the study of malignant disease,³ typhoid fever,⁴ syphilis,⁵ disease of the kidneys,⁶ and other conditions.⁷⁻¹¹

RESULTS

A. *The Weltmann Reaction in Varying Clinical Conditions.*—Short coagulation bands of 5 or less were noted in acute rheumatic fever, with aching of joints with or without swelling or fever, and in some patients with exacerbations of chronic arthritic pains. Some patients had arthritic pains, in the absence of acute rheumatic fever, with a normal coagulation band on one such occasion and a shortened coagulation band on another, while the clinical condition remained apparently the same. The one patient with chorea continued to have a normal coagulation band throughout her illness.

In one patient (History No. 191202), a boy, 8 years of age, a coagulation band of 5 and a corrected sedimentation rate of 6 mm. per hour

were noted after the boy had had epistaxis twice during the preceding week, but appeared otherwise normal. A week later the child was admitted to the hospital with acute rheumatic polyarthritis, and at that time had a sedimentation rate of 32 mm. per hour and a coagulation band of zero. After convalescence the Weltmann reaction returned to a normal range of 6 or 7, and has remained so for over a year. The coagulation band was normal for two weeks before the sedimentation rate reached normal limits. This earlier return of the coagulation band to normal has been noted in other cases of rheumatic fever.⁹

A Weltmann reaction with a coagulation band of 5 was observed in two patients whose throat cultures yielded 25 per cent beta hemolytic streptococci at that time or several weeks earlier. There were one hundred twenty instances of mild colds or coughs without fever, and in four of these a coagulation band of 5 was noted, as compared with an elevated sedimentation rate in forty-six. When there were associated fever and cough, however, seven short coagulation bands were obtained.

In four instances a short coagulation band was found in a pregnant patient, but these same patients had normal coagulation bands at either earlier or later dates during the same pregnancies.

There were two patients with persistently elevated sedimentation rates. The first (History No. 107988) had pelvic thrombophlebitis in 1939. Her sedimentation rate had been elevated long before this, and she suffered with rheumatoid arthritis. She complained of occasional mild discomfort, and had sedimentation rates between 23 and 49 mm. per hour, corrected, during a thirteen-month period of observation in 1940 and 1941. During this time her coagulation band was always 6 or 7, and she was well except for an occasional cold. The second patient (History No. 150784) with a persistently elevated sedimentation rate (12 to 24 mm. per hour, corrected) had a swollen ankle or slightly aching knee at times, and suffered with mild chronic arthritis. However, her coagulation band was reduced (C.B. = 5) only on one occasion, when she had a temperature of 99.4° orally, and swelling and tenderness of a finger joint which were relieved by aspirin.

There was no clinically quiescent patient with a persistently abnormal Weltmann reaction, nor was there a patient with acute rheumatic fever and normal Weltmann reactions at that time. We could discover no relationship between persistently prolonged coagulation bands and the progressive development of rheumatic heart disease in the patients observed during the period of this study.

B. Clinical Significance of Abnormal Coagulation Bands and Elevated Sedimentation Rates.—The results obtained with the Weltmann serum coagulation test and the erythrocyte sedimentation rate will be considered first as to the significance of a normal result, and then as to the significance of an abnormal result.

There were 570 Weltmann tests on the eighty patients with rheumatic heart disease (Table II). Among the 449 Weltmann tests which fell within the normal limits, only twenty-seven, or 6.01 per cent, were obtained when the patients had symptoms or signs of rheumatic activity or other evident disease. Similarly, of the 318 normal sedimentation rates, twenty-two, or 6.97 per cent, were obtained in the presence of clinically evident disease activity which could be expected to be reflected in elevated rates.

TABLE II
ASSOCIATION OF COAGULATION BANDS AND SEDIMENTATION RATES WITH SYMPTOMS

	NO SYMPTOMS	SYMPTOMS	TOTALS
SHORT COAGULATION BAND			
Normal Sedimentation Rate	10	4	
Elevated Sedimentation Rate	9	19	
Totals	19	23	42
NORMAL COAGULATION BAND			
Normal Sedimentation Rate	246	13	
Elevated Sedimentation Rate	176	14	
Totals	422	27	449
PROLONGED COAGULATION BAND			
Normal Sedimentation Rate	40	5	
Elevated Sedimentation Rate	25	9	
Totals	65	14	79
TOTAL			570

Thus, in a single determination a *normal* coagulation band and a *normal* sedimentation rate were equally accurate (93.9 and 93.1 per cent, respectively) in indicating the absence of clinical activity of disease. When the results of these tests were *abnormal*, however, the correlation between the condition of the patient and the Weltmann reaction or sedimentation rate was not so evident.

There were, in all, 252 tests in which the sedimentation rate was elevated. Of these, forty-two, or 16.6 per cent, occurred in association with active disease; the rest were noted after periods of quiescence of the rheumatic process, which has been interpreted as presumably indicating that the disease was still active pathologically. Of seventy-nine Weltmann tests with a shift to the right, there was an incidence of 17.7 per cent in which there were symptoms. The remainder of tests with a prolonged coagulation band were found in cases of clinically inactive disease, and may reflect proliferative healing processes, perhaps eventually resulting in valvular scarring. In contrast, 54.7 per cent of the forty-two Weltmann tests with a shift to the left were associated with clinically evident disease activity.

It is seen that a shift to the left of the coagulation band may mean a clinically active disease process, and a shift to the right a proliferative healing process without evident clinical activity.

On twenty-eight occasions both an elevated sedimentation rate and a shortened coagulation band were present. In nineteen of these tests, or 67.8 per cent, there was evidence of clinical activity.

Five hundred six tests of each type were made when symptoms or signs of active disease were not noted. On such occasions there were 210 elevated sedimentation rates and 84 abnormal coagulation bands. Prolonged coagulation bands were more common than shortened coagulation bands when no symptoms were present. This again suggests that a shift to the right may reflect proliferative healing processes in the absence of clinical activity.

C. Statistical Relationship Between Weltmann Reaction and Sedimentation Rate.—In 610 instances the same specimens of blood were used for a determination of the coagulation band and of the erythrocyte sedimentation rate (Wintrobe method, with correction for volume of packed red cells). The distribution of these results is shown in Table III. Dr. Marie Cakrtova, of the Statistical Department of the Johns Hopkins Hospital, was kind enough to subject these figures to statistical analysis, and her preparation and analysis of Tables IV and V form the basis for this part of the discussion.

TABLE III
COMPARISON OF COAGULATION BAND AND CORRECTED ERYTHROCYTE
SEDIMENTATION RATE

CORRECTED SEDIMENTATION RATE (MM./HR.)	COAGULATION BAND										TOTALS	
	0	1	2	3	4	5	6	7	8	9		10
0-10	0	0	0	0	1	13	115	164	38	7	0	338
11-20	0	0	0	0	1	15	70	53	23	0	0	162
21-30	0	0	0	1	2	8	34	33	9	1	0	88
31-40	1	0	1	1	1	1	4	5	4	1	0	19
41-50	0	0	0	0	1	0	0	1	0	0	0	2
51-60	0	0	0	0	0	0	0	1	0	0	0	1
TOTALS	1	0	1	2	6	37	223	257	74	9	0	610

TABLE IV
COMPARISON OF COAGULATION BAND AND CORRECTED ERYTHROCYTE
SEDIMENTATION RATE

COLUMN NO.	I	II	III	IV	V	VI	VII	VIII	IX	X
	0-5 (SHORTENED C.B.)			6-7 (NORMAL C.B.)			8-10 (PROLONGED C.B.)			
SEDIMENTATION RATE = MM./HR.	NO. TESTS	%	RATE %	NO. TESTS	%	RATE %	NO. TESTS	%	RATE %	TOTAL
0-10	14	29.79	4.14	279	58.12	82.54	45	54.22	13.31	338
11-20	16	34.04	9.88	123	25.62	75.93	23	27.71	14.20	162
21 and over	17	36.17	15.45	78	16.25	70.91	15	18.07	13.64	110
TOTAL	47	100.00		480	100.00		83	100.00		610

% = Percentage of total number of tests with this coagulation band.
Rate % = Percentage of total number of tests with this sedimentation rate.
C.B. = Coagulation band.

The results of the Weltmann serum coagulation test can be conveniently divided into three groups: one with a coagulation band of 0 to 5, inclusive (i.e., a shortened C.B.); one with a coagulation band of 6 or 7 (i.e., a normal C.B.); and one with a coagulation band of 8 to 10 (i.e.,

a prolonged C.B.). The results grouped in this manner are shown in Table IV. The percentage distribution of the sedimentation rates is similar in the normal group (Column V) and in the group with the prolonged coagulation bands (Column VIII). Both of these groups, however, differ from the group with a shortened coagulation band (Column II). The increasing rate percentage in the group with a shortened coagulation band (Column III) suggests that the shorter the coagulation band, the greater the probability of a higher sedimentation rate.

TABLE V
COMPARISON OF OBSERVED AND THEORETICAL DISTRIBUTIONS OF COAGULATION BANDS IN SEDIMENTATION RATE GROUPS

COLUMN NO.	I		II		III		IV		V		VI	
	7.5 (SHORTENED C.B.)		6-7 (NORMAL C.B.)		8-10 (PROLONGED C.B.)							
SEDIMENTATION RATE: MM./HR.	OBSERVED	THEORETICAL	OBSERVED	PERCENTAGE DISTRIBUTION	OBSERVED	PERCENTAGE DISTRIBUTION	OBSERVED	THEORETICAL	OBSERVED	THEORETICAL	OBSERVED	THEORETICAL
0-10	14	27.32	279	58.12	45	48.24						
11-20	16	12.04	123	25.62	23	21.26						
21 and over	17	7.64	78	16.25	15	13.49						
TOTAL	47	47.00	480	100.00	83	82.99						

This fact can be demonstrated more strikingly in another way. In Table V the percentage distribution of the normal group (Column IV) is used as the theoretical distribution, and from this as a standard is calculated the expected number of cases at the different sedimentation rates for the groups with shortened coagulation bands (Column II) and prolonged coagulation bands (Column IV), respectively. The expected number of tests at the different sedimentation rates for the groups with prolonged coagulation bands (Column V) is not far from the observed number for this group (Column V). In the group with shortened coagulation bands, however, the observed distribution (Column I) is quite different from the theoretical distribution (Column II). This difference in the group with a coagulation band of 0 to 5, inclusive, is statistically significant. There is a probability of less than one in one hundred of obtaining such a result by chance alone.

The group with sedimentation rates of 0 to 10, inclusive, is significantly different from the group with rates of 11 to 20, inclusive, and from the combined groups with rates of 11 and over. The last group contributes the most to the statistical significance of the differences between the observed and the expected number of tests.

Thus, there seems to be definite evidence that coagulation bands of 0 to 5, inclusive, are more frequently associated with higher sedimentation rates than are coagulation bands of 6 to 10, inclusive. The usefulness of this conclusion is limited by the fact that for statistical reasons the sedimentation rates over 20 had to be grouped together, leaving a

limited range of sedimentation rates. More extensive experience may demonstrate the relationship between lower coagulation bands and higher sedimentation rates on a more gradual scale.

DISCUSSION AND CONCLUSIONS

To ascertain the value of the Weltmann serum coagulation test in detecting occult rheumatic activity, two things must be done. First, the variation in the coagulation band with easily recognized signs of disease activity should be determined, measuring the ability of the test to confirm known signs of rheumatic activity; for, if the Weltmann test does not confirm obvious manifestations, its value in indicating occult processes is open to debate. After the sensitivity of this reaction to recognized clinical activity is thus ascertained, the next problem is to evaluate its usefulness in indicating occult rheumatic activity.

The results in this series seem to show that a *normal* sedimentation rate and a *normal* coagulation band are equally significant in indicating the absence of clinical disease activity, as demonstrated by their infrequent association with signs or symptoms of an active disease process. An *abnormal* Weltmann reaction, especially a short coagulation band, was more frequently associated with clinical disease activity than was an elevated sedimentation rate. The larger proportion of elevated sedimentation rates in the absence of clinical activity would suggest that an *abnormal* Weltmann result would be a more reliable indicator of the presence of an active process, and that this test would be of value in detecting possible subclinical inflammatory activity, such as may exist in patients with progressive rheumatic heart disease.

The second aspect of the problem defined earlier would involve prolonged observation of a group of patients, to see whether patients with abnormal coagulation bands developed rheumatic heart disease more frequently than those with normal coagulation bands, in the absence of easily recognized signs of rheumatic activity. Only in this way could one draw valid conclusions as to the value of this test in detecting occult or subclinical rheumatic activity. This report covers only the first phase of the problem as described above, and certain other of our results.

While the period of study of these cases has been insufficient to draw any conclusion as to the relationship between a persistently lengthened coagulation band, a normal coagulation band, or a shortened coagulation band and the rate of progression of the rheumatic process, the results thus far obtained suggest that this test may be of value in pursuing such a study. It is suggested that the Weltmann serum coagulation test be used, not to supplant the erythrocyte sedimentation rate in the study of rheumatic fever and the development of rheumatic heart disease, but as an added procedure, based upon certain changes in the blood proteins, which may shed light upon the still unknown underlying process.

The infrequent occurrence of a shortened coagulation band in association with colds and coughs in the absence of fever, and the presence of a Weltmann reaction with a shift to the left when fever is added to these symptoms, suggest that inflammation and changes in the blood proteins are present under the latter circumstances, and indicate another application of the Weltmann test.

The significant correlation between shortening of the coagulation band and elevation of the erythrocyte sedimentation rate, pointed out in part C of the RESULTS, fits in with several other interesting observations. Shedlovsky and Scudder¹² made a comparison of erythrocyte sedimentation rates and electrophoretic patterns of normal and pathologic human blood, and noted that "an increase of alpha globulin seems to take place, as well as an increase in sedimentation rates, when there is present any considerable inflammation or tissue destruction, irrespective of its cause." They presented a graphic correlation between sedimentation rates and alpha globulin levels. Scherlis and Levy,¹³ investigating the mechanism of the Weltmann serum coagulation test, showed that the length of the coagulation band depends upon qualitative rather than quantitative changes in the blood serum. They subjected the same specimen of blood to an electrophoretic analysis and a Weltmann test in thirty-three instances, and demonstrated an inverse relationship between the percentage of alpha globulin in the blood and the length of the coagulation band.

Thus, while one group noted that an elevated sedimentation rate seems to be associated with an increase of alpha globulin, another group demonstrated that a shortening of the coagulation band is associated with an increase of alpha globulin. The present paper independently points out the statistically significant correlation between elevated sedimentation rates and shortened coagulation bands. It would seem very likely, therefore, that a somewhat similar, although not identical, mechanism underlies both tests.

The lack of correlation between prolongation of the coagulation band and elevation of the sedimentation rate may be explained by the fact that a lengthening of the coagulation band is related to a *decrease* in the percentage of alpha globulin and an accelerated sedimentation rate has been shown to be related to an *increase* in alpha globulin. Perhaps both tests are largely dependent upon variations in the alpha globulin of the blood, but the Weltmann reaction is more sensitive over the range where alpha globulin percentages are lowest.

SUMMARY

1. The variation of the Weltmann reaction with different clinical conditions in patients with actual or potential rheumatic heart disease has been described.

2. There was no patient with clinically quiescent disease with a persistently abnormal Weltmann reaction, nor was there a patient with acute rheumatic fever and normal Weltmann reactions at that time.

3. There was no relationship between persistently prolonged coagulation bands and the progressive development of rheumatic heart disease in the patients observed during the course of this study.

4. In a single determination, a normal coagulation band and a normal sedimentation rate were equally accurate (93.9 and 93.1 per cent of 449 tests, respectively) in indicating the absence of clinical disease activity.

5. An abnormal Weltmann reaction, especially a shortened coagulation band, was more frequently associated with clinical disease activity than was an elevated sedimentation rate.

6. The statistically significant correlation between elevated sedimentation rates and shortened coagulation bands was pointed out, and the relationship of these results to an increase in alpha globulin in the blood was discussed.

The authors are indebted to Dr. Bernard Davis for the electrophoretic analysis of the blood sera, and to Dr. Caroline Bedell Thomas and Dr. John A. Leutscher for suggestions and criticisms.

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ROENTGENOLOGIC AND ELECTROCARDIOGRAPHIC CHANGES IN THE NORMAL HEART DURING PREGNANCY

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MANY women who are examined for the first time late in pregnancy present clinical evidence of questionable cardiac enlargement, symptoms and signs suggestive of myocardial insufficiency, such as dyspnea, edema of the ankles, and possibly occasional râles at the base of the lungs, and, in roughly 10 per cent, an apical systolic murmur and an accentuated pulmonic second sound. It is important for the obstetrician to know whether organic heart disease exists, for the management of protracted labor or possible dystocia will most certainly be influenced by such a diagnosis. Whether or not the heart is able to support the load of pregnancy and carry the patient successfully through labor is often difficult to ascertain clinically, and various laboratory procedures have been suggested to determine the severity of the cardiac state. The methods most frequently employed are the roentgenogram and the electrocardiogram. All patients referred for consultation to the Cardiac-Obstetrical Clinic from the Prenatal Clinics have roentgenograms in the three standard positions, posteroanterior, left oblique, and right oblique, with esophagram, before being examined in the Cardiac Clinic. During the past five years, we have been impressed by the frequency of roentgenologic reports of "enlargement of the left auricle in the right oblique view and straightening of the left upper border of the heart on the posteroanterior view, compatible with the diagnosis of mitral valvular disease" on patients who presented no definite history, symptoms, or signs of organic heart disease. A search of the literature failed to reveal any observations on encroachment on, or backward displacement of, the esophagus associated with pregnancy, and there was considerable divergence of opinion as regards the cause of such changes as have been reported in the roentgenogram and electrocardiogram. Most investigators agree that the heart shadow increases in size during pregnancy, but whether this is as a result of essential cardiac hypertrophy, with or without dilatation, as suggested by Jensen and Norgaard¹ and their chief, Gammeltoft,² or whether it is produced primarily by rotation and displacement of the heart, as suggested by most American workers, particularly Hamilton³ and his co-workers, is still undecided.

In 1922, Smith⁴ observed the presence of left axis deviation in the electrocardiogram of a woman who was eight months pregnant. He followed her throughout her labor and noted that, with descent of the fetus, this became less marked. Thirty minutes post partum it had

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completely disappeared. McIlroy and Rendel,⁵ Konki,⁶ Jensen and Norgaard,⁷ and Carr, Hamilton, and Palmer⁷ have recorded similar observations. Pardee⁸ was the first to describe a deep Q wave in Lead III of the electrocardiogram, and Konki⁶ and Carr and Palmer⁹ noted inversion of the T wave in Lead III during the later months of pregnancy. These observations have been variously interpreted, but, in general, two schools of thought exist: that these changes are a result of cardiac hypertrophy and dilatation, or that they indicate displacement and rotation of the heart.

The literature on roentgenologic changes in the heart during pregnancy is even more confused. Gerhardt¹⁰ observed that during the later months of pregnancy the heart assumed a mitral shape. Hyeman¹¹ stressed the elevation of the diaphragm and the transverse position of the heart during the third trimester. This was discounted by Jensen and Norgaard, who found an increase in the diameters of the heart in, roughly, one-third of their cases. Hamilton and Thomson³ emphasized not only the general enlargement of the heart, but also the increase in the so-called normal hilar markings which may be mistaken for abnormal pulmonary congestion by one unfamiliar with the roentgenograms of pregnant women. Landt and Benjamin¹² called attention to the encroachment on the anterior clear space by the right ventricle in the lateral view.

In view of the vast differences of opinion, and the fact that no definite conclusions may be drawn from the work quoted, it was thought that a resurvey of the problem, using slightly different techniques, was warranted.

For purposes of study, patients who were in the first trimester of their pregnancy, and had no history, signs, or symptoms of heart disease were referred to us from the prenatal clinics. They were then examined by us to confirm the opinion that they were perfectly normal. Serial roentgenograms in the three standard positions were taken and repeated at three-month intervals during their gestation, and one and two or more months post partum. Electrocardiograms, using the two-string electrocardiograph and thus securing Leads I and III simultaneously, in order to calculate accurately the electrical axis, were also taken, and these were repeated at four-week intervals. All patients who did not continue under our observation for their entire pregnancy and post-partum period were excluded from the study group. A large number of cases were observed, but only eighteen were followed throughout the desired period, and this is the group reported. All the observations on the others confirmed those in this group.

Electrocardiographic Changes.—The most outstanding changes in the electrocardiogram were confined to Lead III. A prominent and, at times, deep Q wave and inversion of the T wave were present in five cases, and the T wave became negative and then positive post partum without alteration of the Q wave in four cases. No abnormalities of QRS or the RS-T segments appeared. Although there was no absolute

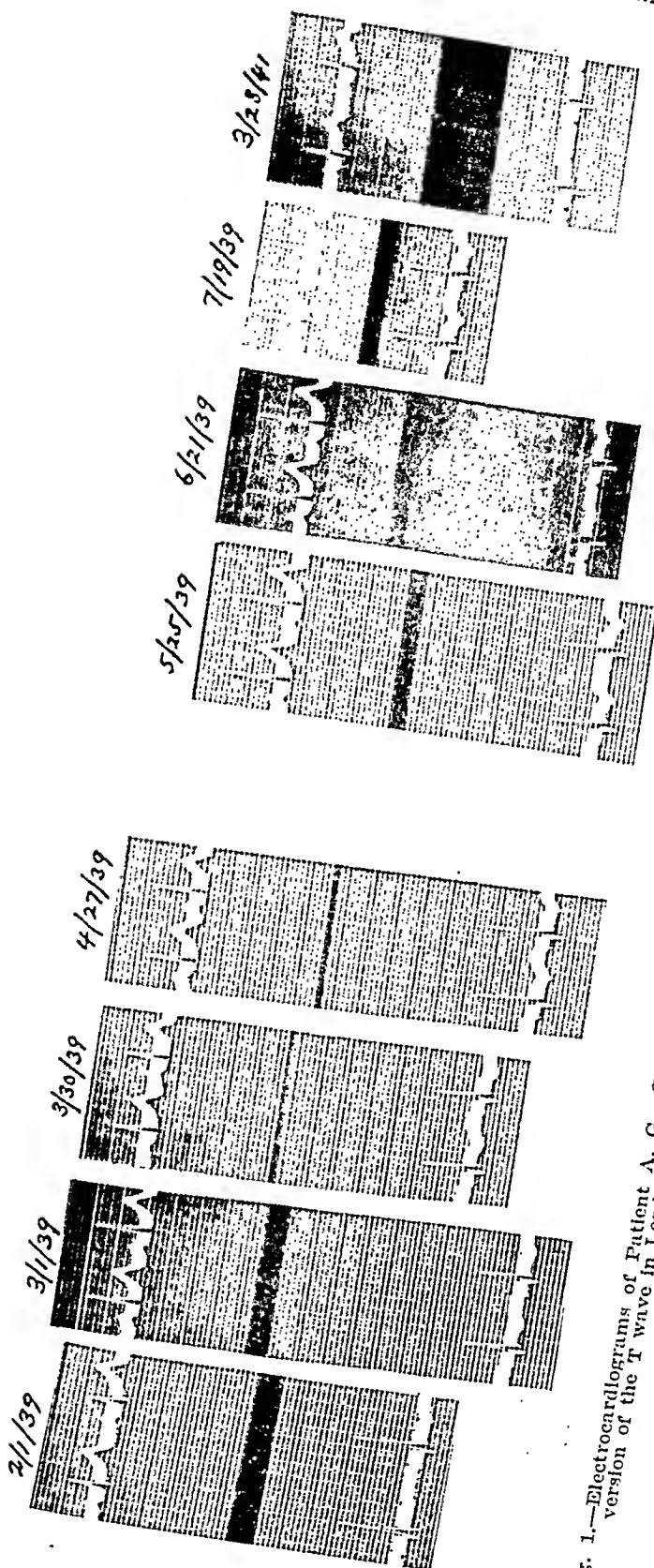


Fig. 1.—Electrocardiograms of Patient A. G., Case No. 9. Patient delivered of normal full-term baby on Aug. 31, 1939. Note the inversion of the T wave in Lead III; it returned to normal post partum. The Q wave was constant throughout in this lead.

or invariable rate of electrical axis deviation, nevertheless the trend for the group confirmed the observations of Carr and Palmer³ that the axis undergoes a shift toward the left during the first and second trimesters of pregnancy, and then swings to the right. This change in the angle of the axis was not pronounced on superficial inspection of the electrocardiograms, but when measurements were made, and the angle of axis direction was plotted according to Carter, Richter and Greene's¹² modification of the Einthoven method, the shift was obvious. In a few instances the difference of the angle varied as much as 28 degrees, but in most instances the magnitude of the shift was, roughly, 15 degrees (Table I, Figs. 1 and 2).

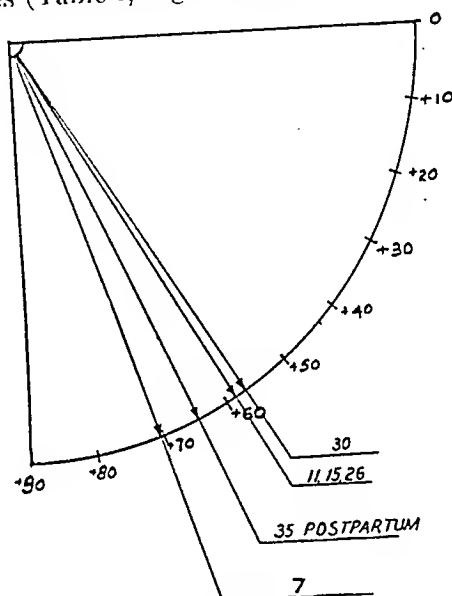


Fig. 2.—Patient M. S., Case 18. Illustration of the shift of the angle of the electrical axis in a rather characteristic fashion. The numbers on the arrows indicate the time of gestation in weeks.

TABLE I
ELECTROCARDIOGRAPHIC OBSERVATIONS

CASE NUMBER	PATIENT	MINIMUM ANGLE (DEGREES)	MONTH	MAXIMUM ANGLE (DEGREES)	MONTH	Q ₂ -T ₂ CHANGES
1	L. H.	77	4	59	8	Deep Q, negative T
2	K. R.	27	3	9	4	
3	C. M.	43	3	22	6	
4	A. F.	73	3	43	7	
5	S. K.	-11	4	-16	7	Negative T
6	F. O'H.	31	3	10	7	
7	T. R.	24	3	-15	4½	
8	V. B.	9	3	-½	4	
9	A. G.	71	3	56	4	Negative T
10	E. P.	45	3	17	8	Deep Q, negative T
11	M. G.	35	3	26	6	
12	D. P.	75	3	54	5	Deep Q, negative T
13	M. H.	75	4½	62	7	Deep Q, negative T
14	E. C.	13	7	-14	6	Negative T
15	R. G.	9	3	-½	6	
16	B. P.	14	3	11	7	
17	B. D.G.	45	3	36	9	
18	M. S.	71	2	51	7	Deep Q, negative T



Fig. 3.—Roentgenograms of Patient A. G., Case 9. Patient ten weeks pregnant.



Fig. 4.—Roentgenograms of Patient A. G., Case 9. Patient twenty-six weeks pregnant. Note the invasion, and moderate displacement backwards, of the esophagus in right anterior oblique view.

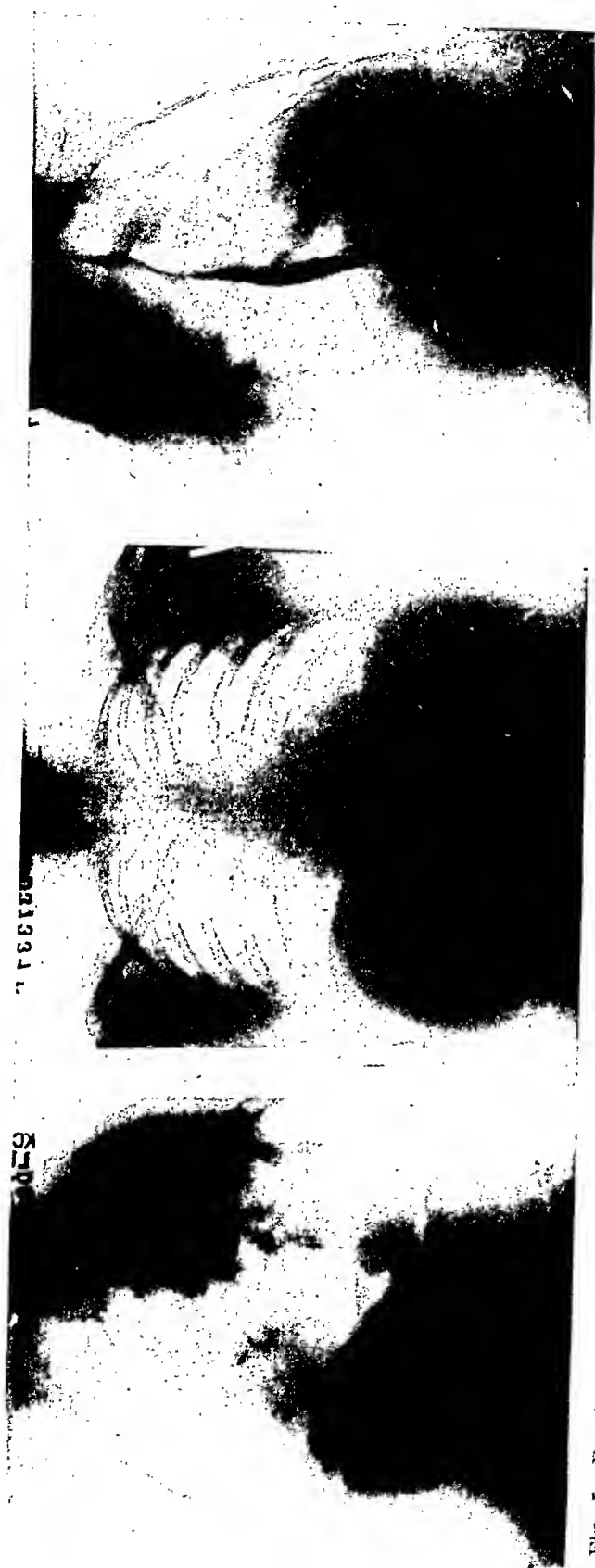


Fig. 5.—Roentgenograms of Patient A. G., Case 9. Patient thirty-four weeks pregnant. Note the marked change in the esophagus as compared to Fig. 4.

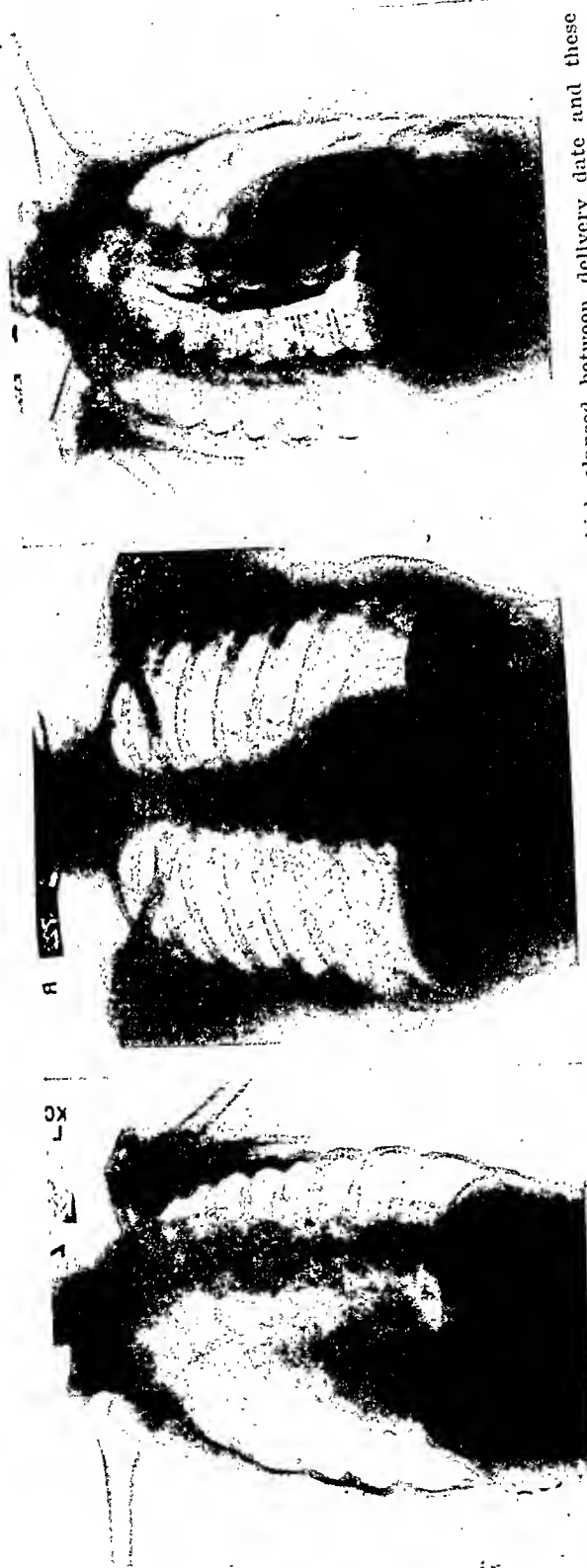


Fig. 6.—Roentgenograms of Patient A. G., Case 9. Post partum. The length of time which elapsed between delivery date and these roentgenograms was due to difficulty in getting the patient to return.

TABLE II
ROENTGENOLOGICAL OBSERVATIONS

CASE NUMBER	PATIENT	STRAIGHT- ENING OF LEFT BORDER	PROMINENCE OF PUL- MONARY CONUS	INVASION OF ANTERIOR WALL OF ESOPHAGUS	MARKED ENCROACH- MENT ON ESOPHAGUS	ELEVATION OF LEFT MAIN BRONCHUS
1	I. H.			Y		
2	K. R.			Y	Y	
3	C. M.			Y		
4	A. F.	Y		Y		
5	S. K.			Y		
6	F. O'H.		Y			
7	T. R.				Y	
8	V. B.					
9	A. G.			Y		
10	E. P.					
11	M. G.	Y	Y			
12	D. P.		Y	Y		
13	M. H.			Y		
14	E. C.					Y
15	R. G.					
16	B. P.					
17	B. DiG.					
18	M. S.					

Y represents the occurrence of a change.

Roentgenologic Changes.—Several distinct changes were noted in the roentgenograms, and these have been tabulated (Table II). The most frequent abnormality was an encroachment on the anterior surface of the esophagus in the region of the left auricle. In the majority of instances the esophagus as a whole was not displaced, but a definite indentation of the anterior wall was seen (Figs. 3, 4, 5, and 6). There were ten such instances, but in two subjects there was marked invasion, with moderate backward displacement of the barium-filled esophagus. There were two instances of straightening of the left upper border of the cardiac silhouette, and three instances of prominence of the pulmonary conus.

DISCUSSION

Previous roentgenologic studies of the heart in pregnancy have been limited primarily to posteroanterior views. Landt and Benjamin¹² mention encroachment on the anterior clear space by the right ventricle. Studies in the oblique positions have been found to be particularly valuable in demonstrating cardiac enlargement in persons with short, broad chests. It therefore seemed probable that the right oblique position, with an esophagram, might be similarly useful in studies of pregnant women. Clauser¹⁴ found a suggestion of generalized enlargement of the heart, with an increasing tendency toward a transverse position and kinking of the great vessels. Jensen¹ studied 157 women roentgenologically from the onset of pregnancy until the end of the puerperium, using the posteroanterior view. He found that 33 per cent of these women had a demonstrable increase in the cardiac diam-

eters. This occurred before the elevation of the diaphragm took place. This change was not constant, and was more likely to be present in those women who were suffering from what he terms "gestatory heart disease." In his electrocardiographic studies, he attributed the reduction in the amplitude of the R wave and the increase in the depth of the S wave in Lead III, with a resultant shift in the electrical axis, and the early occurrence of this change, to hypertrophy and dilatation. Most investigators disagree with this. Although it has been shown^{15, 16} that the cardiac output is increased from one-third to one-half during the latter part of pregnancy, it is also true that moderately increased cardiac work does not necessarily lead to hypertrophy of the normal heart. Furthermore, it has been demonstrated that no observable cardiac hypertrophy is found in the guinea pig, cat, or dog, during pregnancy.¹⁷ The appearance of a Q wave and the negativity of the T wave in Lead III are easily explained as a result of a positional shift of the heart. Cohn and Raisbeck,¹⁸ by rotating leads taken directly from the chest in a clockwise manner through an arc from 80 to 120 degrees, produced curves showing typical, large Q waves in Lead III. Inversion of the T waves in this lead similarly indicates a change in the position of the heart. The inconstancy of these changes weakens the argument for hypertrophy, for this should be present in all or a majority of pregnant women. In the cases studied, although rather marked changes occasionally occurred, the patients never manifested any evidence of heart disease. A further point against hypertrophy is that often these changes disappear toward the end of pregnancy, when there is no reason to believe that hypertrophy should cease. It seems more logical to attribute the observed changes to displacement upwards and laterally, with rotation around the long axis of the heart. The relation of the long and transverse diameters of the chest to the transverse diameter of the heart during pregnancy will influence the degree of shift which occurs. Thomson, Cohen, and Hamilton,¹⁹ in comparing the relationship of the electrocardiographic changes in the different types of chest, found that the Q- and T-wave alterations were more evident when the height of the diaphragm most markedly affected the position of the heart.

In reviewing our roentgenograms we were impressed by the similarity of the changes associated with pregnancy and those encountered in mitral disease. The posteroanterior view of the heart in mitral stenosis almost invariably presents a characteristic appearance. Its chief distinguishing features are straightening or bulging of the left upper border as a result of prominence of the pulmonary conus and the left auricle. Other abnormalities include elevation of the left main bronchus by the enlarged left auricle, the engorged pulmonary veins, or both, increased hilar shadows due to the dilated pulmonary artery branches, and clouding of the lung fields caused by pulmonary congestion. The

fact that the left upper border of the cardiac silhouette may become straightened during pregnancy in normal women is so well known that Gerhardt's phrase "mitral shape without mitral lesion" has been used to describe the picture.¹⁰ Lately, particular attention has been directed to the use of roentgenologic methods in the differentiation of enlargement of the individual chambers of the heart, and, in this connection, study of the barium-filled esophagus in the right oblique position is considered of paramount importance in the diagnosis of the enlargement of the left auricle which is so commonly associated with mitral disease. Evans²⁰ states that "the alteration of the form of the impression (i.e., left auricle) in the right oblique view in mitral stenosis is acknowledged as a valuable sign. Moderate distension of the left auricle produces a conspicuous left auricle impression in the right oblique position, but the significance of slight prominence of the impression is often difficult to assess. When adjudicating whether the curve is normal or abnormal in the adult, it is necessary to pay particular attention to the upper segment of the impression because abruptness of this portion of the curve is caused by the atrial prominence of the left auricle. This is fed by the pulmonary veins which become distended in mitral stenosis. Thus, the barium meal is slightly delayed at the commencement of the impression and produces a sharp angulation to the right as viewed in this position." Recent investigations have shown that backward displacement of the esophagus in this position is not invariably caused by left auricular enlargement,²¹ but may be the result, in a small percentage of cases, of a variety of conditions, e.g., congenital heart disease, aortic insufficiency, hypertension, auricular fibrillation, complete heart block, and aneurysm of the heart. It may also be present during gestation in normal women. In two of the eighteen women in the present series this phenomenon was conspicuous, and in eight of the others it was present in a lesser degree.

It seems possible to account for the indentation of the esophagus by some generalized increase in the size of the heart during pregnancy. The work of Thomson, Hirsheimer, Gibson, and Evans²² has shown that the total blood volume increases from early pregnancy to the ninth lunar month; during the tenth month there is a definite diminution, and by the second month of the puerperium it has been restored to the normal level. The time at which the reduction takes place is usually the thirty-fourth to the thirty-sixth week. Burwell and his co-workers²³ demonstrated that the cardiac output shows a similar trend of comparable magnitude. In our roentgenograms which were taken at the thirty-fourth week, the esophageal indentation that had been present earlier in pregnancy had practically disappeared. This suggests that the increase in blood volume causes cardiac enlargement by increasing the quantity of blood in the heart. Our studies lend no support to the view that cardiac hypertrophy occurs during normal pregnancy. If the enlargement were due to hypertrophy, one would

expect, if it could occur at all, a gradual decrease in size, rather than the relatively sudden change which takes place at a particular time in the pregnancy.

CONCLUSIONS

1. Eighteen pregnant women were followed from the early months of pregnancy to the post-partum period by serial roentgenographic studies in the posteroanterior and left and right oblique views, with esophagrams, and, also, by monthly electrocardiograms, using a two-string galvanometer to measure the changes in the electrical axis accurately.

2. The outstanding roentgenologic change was an indentation of the anterior wall of the esophagus. This is attributed to an increase in the size of the heart as a result of the increased amount of blood it contains, in consequence of the increased blood volume. The transverse diameter of the heart was increased during pregnancy, but, as the diaphragm becomes elevated, it is difficult to assess the relative value to be placed on shift of position and increase in blood volume.

3. The principal electrocardiographic changes were the frequent development of a deep Q wave and negative T wave in Lead III. The electrical axis changed, on the average, about 15 degrees. The reason for so slight a change when, roentgenographically, the position of the heart would suggest a much greater shift in the axis may be attributed to the fact that the heart is not only shifted transversely, but is also rotated in its long axis.

We wish to express our appreciation for the assistance rendered by Miss Eveline D. Reynolds, who took the electrocardiograms, and to Dr. Richard A. Rendich, Director of the X-Ray Department of the Kings County Hospital.

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THE EFFECT OF TRICHLORETHYLENE ON THE HUMAN, CANINE, AND RABBIT ELECTROCARDIOGRAM

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ALTHOUGH trichlorethylene has been used in the treatment of angina pectoris,^{1,2} its action on the cardiovascular system has not been extensively investigated. Only two short reports dealing with its cardiovascular effects are available,^{3,4} and both came from the same group of workers. Since trichlorethylene may be useful in the prevention and treatment of angina pectoris, an extensive study of its action was undertaken. In this paper the electrocardiographic changes produced by the administration of trichlorethylene to human, canine, and rabbit subjects are reported.

EXPERIMENTS

Rabbit Studies.—In these experiments control electrocardiograms were taken after the animals had been resting in a basal-like state for fifteen minutes, and test records were taken during and after the inhalation of trichlorethylene. In the first three experiments, normal rabbits, not previously used for any kind of experimentation, were used, whereas, in the last two, the rabbits had been anesthetized with trichlorethylene every day for a week. All of the rabbits were practically of the same weight (5 to 6 pounds). In this way, the effects of trichlorethylene on the electrocardiograms of rabbits never before anesthetized and on rabbits subjected to repeated anesthetization were studied.

Fig. 1 presents a series of records obtained from a rabbit which had never before been anesthetized with trichlorethylene. *A* is the control record; *B* and *C* were made after 1 c.c. of trichlorethylene had been given by inhalation, *D*, *E*, and *F*, after another cubic centimeter had been given by inhalation, *G*, after trichlorethylene had been discontinued for about five minutes, and *H*, after trichlorethylene had been discontinued for about fifteen minutes. The following effects may be observed: marked slowing (*B* and *C*), pulsus bigeminus (*D*), and extrasystoles (*F*).

The records presented in Fig. 2 were obtained from the rabbit of Fig. 1 after the animal had been subjected to daily anesthetization for a week. *A* is the control record; *B*, *C*, *D*, *E*, *F*, and *G* were taken after 2 c.c. of trichlorethylene had been administered by inhalation, and *H*, after trichlorethylene had been discontinued for about fifteen minutes. The effects in this experiment include marked slowing (*B*, *C*, *D*, *E*, *F*, and *G*), inversion and obliteration of the P wave (*D* and *G*), and changes in the T wave—diplasic to inverted (*D*, *E*, and *F*).

Canine Studies.—Four dogs, which weighed 35 to 40 pounds, were used in these experiments. They were anesthetized with nembutal, and electrocardiograms were made before and after trichlorethylene was given while the blood pressure, respiration, and kidney volume were being recorded on a kymograph. The effects of trichlorethylene on the blood pressure, respiration, and kidney volume of the dog will be dealt with in another paper. Trichlorethylene was administered in 1 c.c. amounts, approximately five minutes apart, first by inhalation, and then intravenously at about ten-minute intervals.

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In three of the dog experiments the effects of different concentrations of trichlorethylene were looked for. Giving too much of the drug was avoided because we wanted the animals to survive. In the other experiments (two), the effects of the quantity of the drug necessary to kill the animals were studied.

Fig. 3 includes a sequence of electrocardiograms from a dog that was used in the first series of experiments. *A* is the control record, *B* was taken after 6 c.c. of trichlorethylene had been administered by inhalation, *C*, after 1 c.c. of trichlorethylene had been given intravenously, *D*, after the second cubic centimeter had been given intravenously, *E*, after the third cubic centimeter had been given intravenously, and *F*, *G*, and *H*, after the fourth cubic centimeter had been given intravenously.

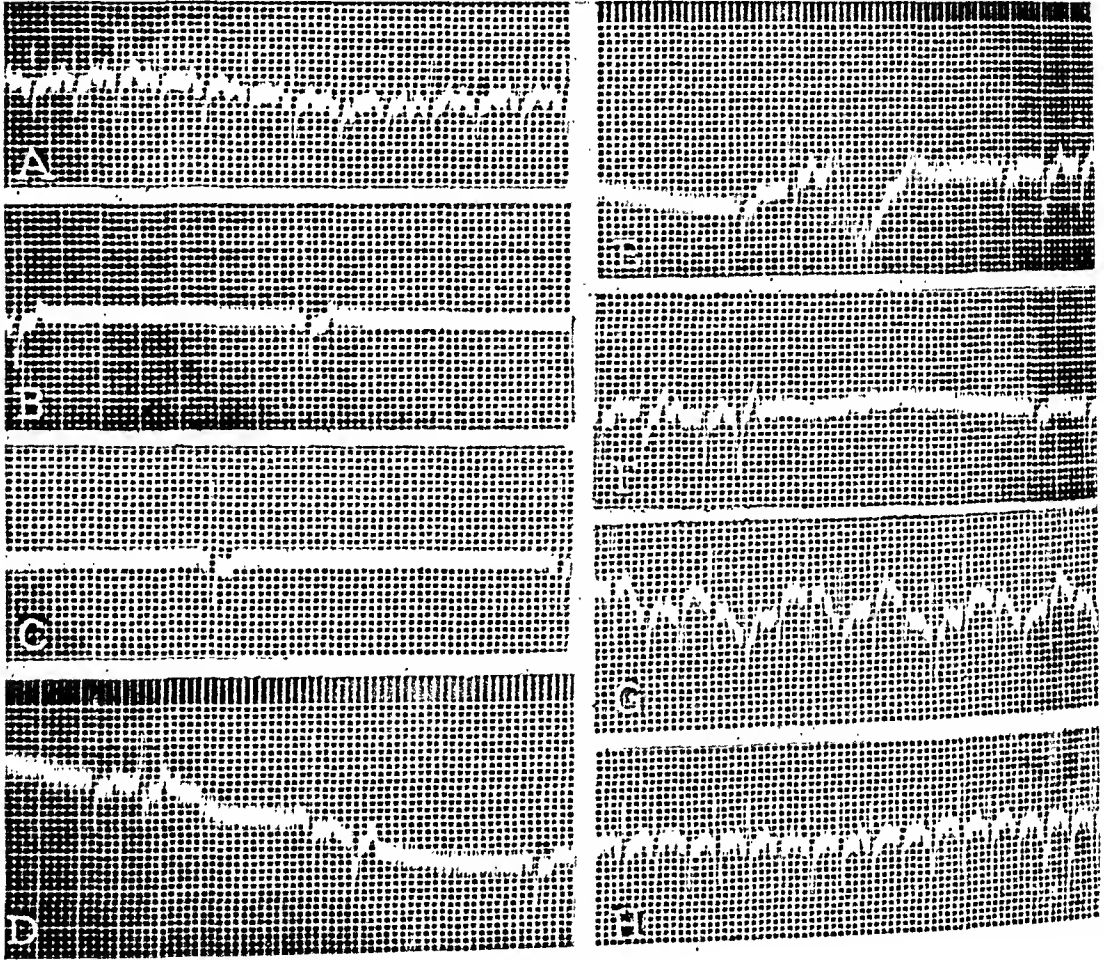


Fig. 1.

Study of these records reveals that significant electrocardiographic changes did not occur, even after 6 c.c. of trichlorethylene had been given by inhalation (*A* and *B*). Noteworthy electrocardiographic changes occurred in this experiment only after the drug had been given intravenously (*C* to *H*, inclusive). In *C* the rate is slower; in *D* the rate is slower still, and there are changes in the P wave; in *E* an ectopic beat occurs; in *F* and *G* the P wave is smaller; and in *H* the P wave is isoelectric.

The electrocardiograms presented in Fig. 4 were obtained from a dog in the second series of experiments. *A* is the control record, *B* was made after 5 c.c. of

trichlorethylene had been administered by inhalation, *C*, after 1 c.c. of trichlorethylene had been injected intravenously, *D*, after 3 c.c. of the drug had been injected intravenously, *E*, *F*, and *G*, after the sixth, seventh and eighth cubic centimeter of the drug had been injected, and *H*, as the dog died.

The electrocardiographic changes in this experiment were similar to those in Fig. 3, except for the changes associated with the death of the animal. Pulsus bigeminus (*C* and *D*) and complete block at the auriculoventricular node (*E*, *F*, and *G*) are the outstanding abnormalities in Fig. 4. The auriculoventricular block produced in this experiment was very likely associated with the large amount of trichlorethylene administered.

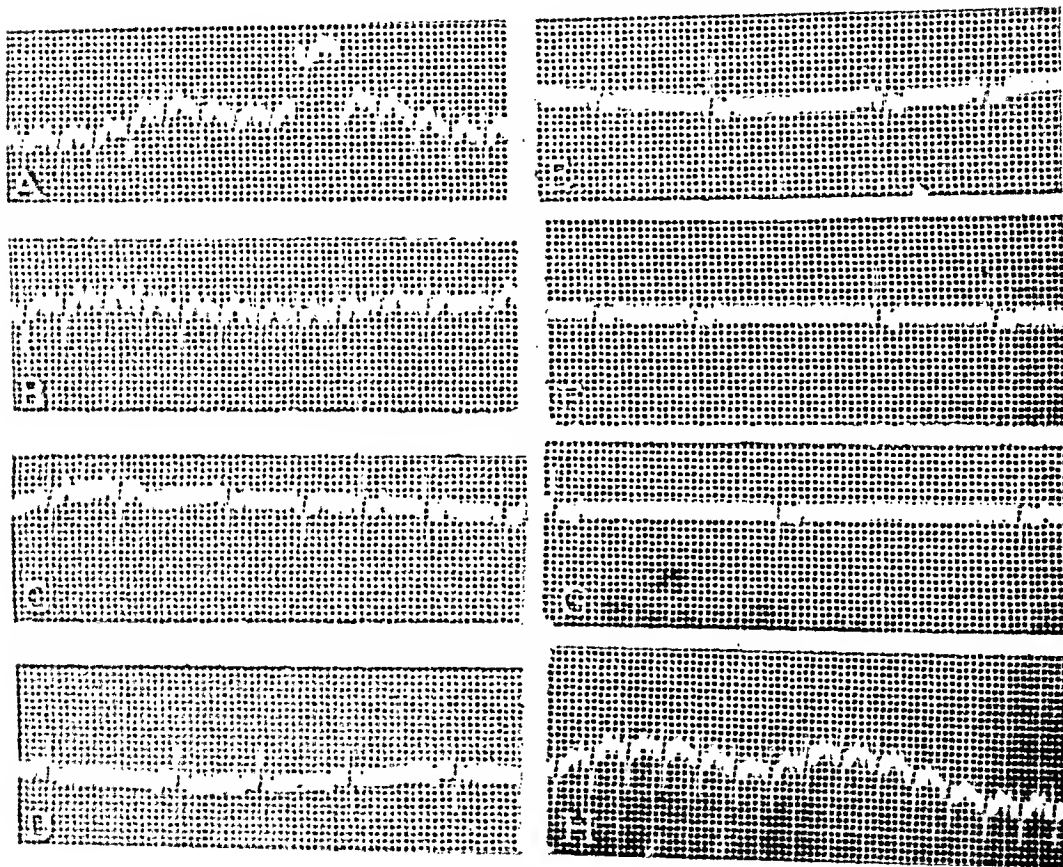


Fig. 2.

Human Studies.—The possible effects of a therapeutic dose of trichlorethylene (four to six deep inhalations from an ampoule broken in a kerchief) were watched for in these experiments. Six normal subjects and ten patients with cardiovascular disorders were employed. Electrocardiograms, sphygmograms, and blood pressure readings were taken before and after trichlorethylene was administered to the normal subjects. No sphygmograms were obtained from the subjects with cardiovascular disease.

The blood pressure readings presented in Table I were obtained from the normal subjects. Except in Subjects A and C, no significant changes in blood pressure took place after trichlorethylene was administered. Similarly, no significant changes

were observed in the electrocardiograms and sphygmograms from these subjects. The control and test sphygmogram and electrocardiogram from Subject B, reproduced in Fig. 5, illustrate these points.

The inhalation of trichlorethylene also did not produce any noteworthy changes in the blood pressure or electrocardiograms of the subjects with cardiovascular disease. Their blood pressure readings are given in Table II. Fig. 6 presents the electrocardiograms of Subject F.

TABLE I
BLOOD PRESSURE MEASUREMENTS ON NORMAL SUBJECTS

SUBJECT	SEX	AGE (YR.)	BLOOD PRESSURE*	
			BEFORE	AFTER
A	M	34	110/62	92/70
B	M	40	135/95	130/95
C	F	28	134/90	120/84
D	M	28	120/84	120/70
E	M	37	126/90	120/90
F	F	27	124/86	124/76

*Before and after the inhalation of trichlorethylene.

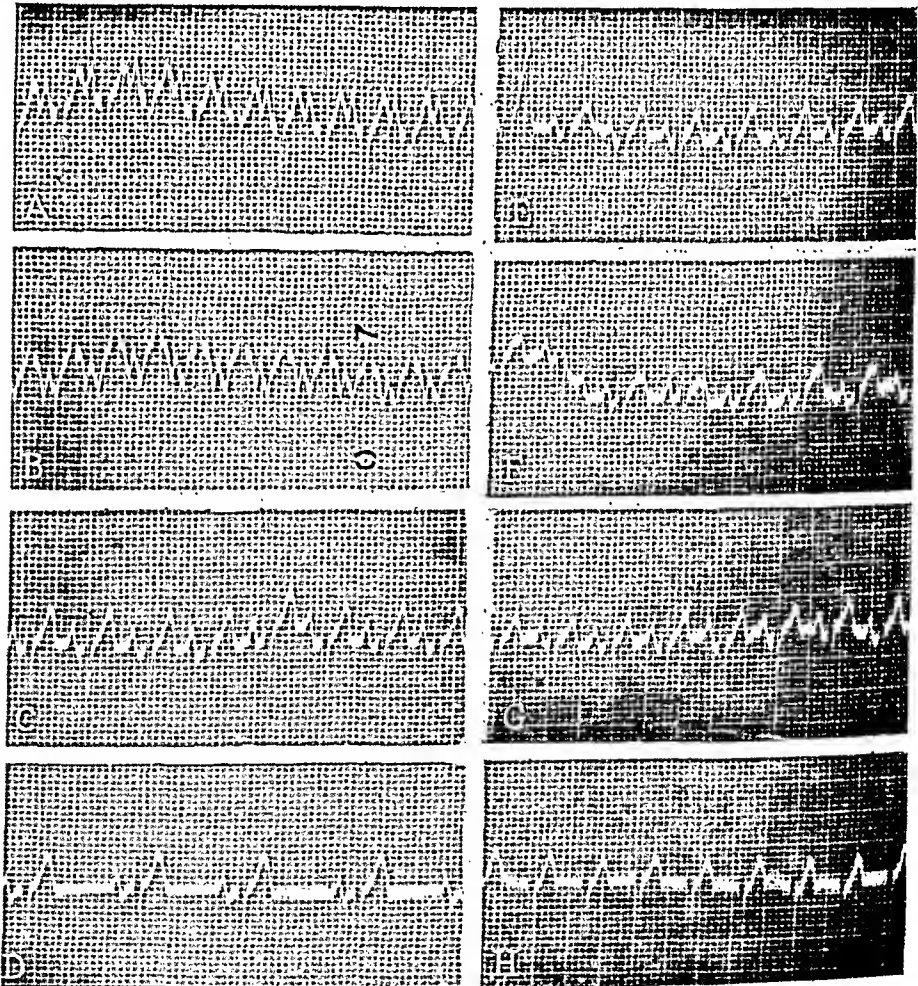


Fig. 3.

TABLE II

BLOOD PRESSURE MEASUREMENTS ON SUBJECTS WITH CARDIOVASCULAR DISEASE

SUBJECT	SEX	AGE (YE.)	DISEASE	BLOOD PRESSURE*	
				BEFORE	AFTER
A	M	68	Arteriosclerosis	115/80	120/80
B	F	22	Paroxysmal tachycardia (amputation of left leg because of embolism)	135/100	140/110
C	F	68	Varicosities of lower ex- tremities	150/100	150/100
D	F	56	Varicosities of lower ex- tremities	120/80	110/70
E	M	56	Arteriosclerosis (Diabetes)	200/110	200/110
F	F	67	Arteriosclerosis	190/80	190/80
G	M	59	Thromboangiitis obliterans	135/85	140/80
H	M	64	Arteriosclerosis, angina pec- toris, myocarditis	150/85	165/85
I	F	65	Arteriosclerosis	190/120	185/120
J	M	65	Varicosities of lower ex- tremities	145/80	140/80

*Before and after the inhalation of trichlorethylene.

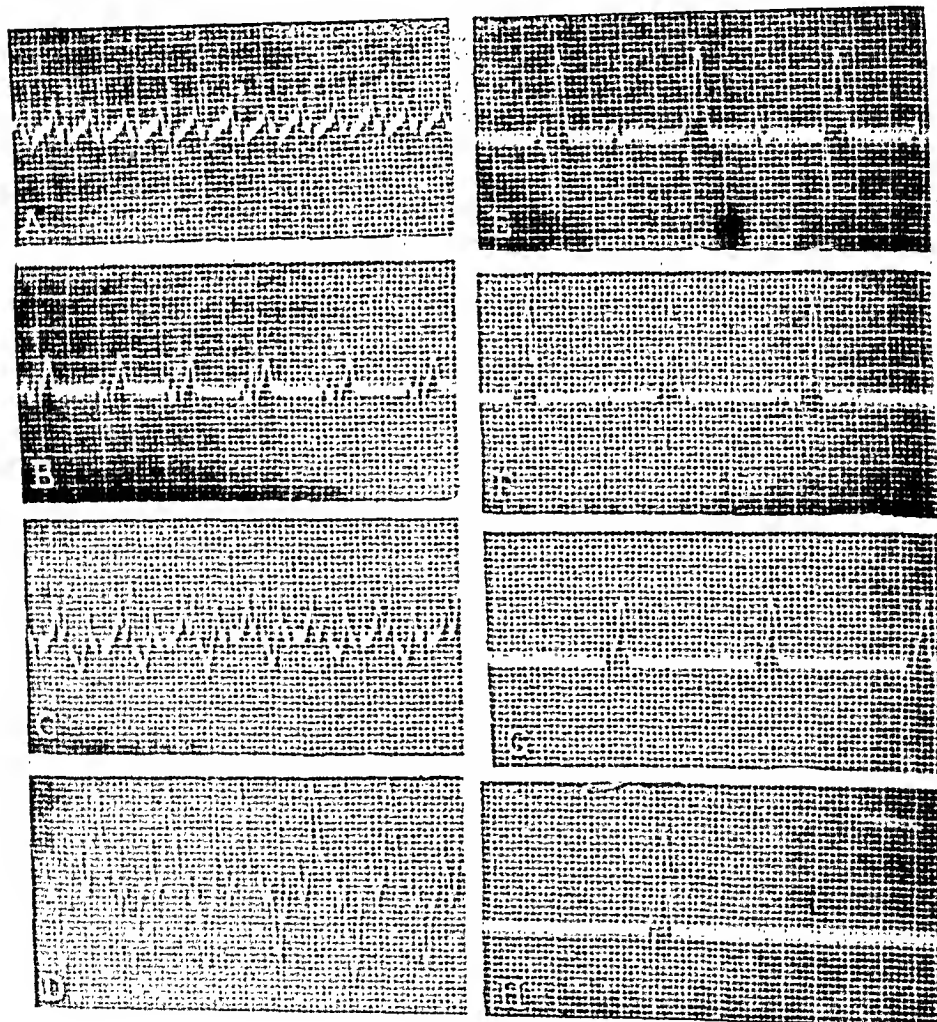


Fig. 4.

DISCUSSION

The electrocardiograms obtained from the rabbits which had never before been anesthetized with trichlorethylene and from those subjected to repeated anesthetization indicate that the drug affects the conducting mechanism and the muscle of the rabbit's heart. Evidence that there is an alteration in the conducting mechanism lies in the marked slowing and ectopic beats. Obliteration of the P wave and the changes in the T wave, on the other hand, are indications of its effect on the myocardium, especially since these changes were observed in the electrocardiograms obtained from the rabbits that were subjected to repeated anesthetization. Permanent electrocardiographic changes were not observed. Return to normal took place when the drug was withdrawn. Nevertheless, since P and T wave changes occurred after the rabbits had received trichlorethylene repeatedly, there is a possibility that permanent changes may take place.

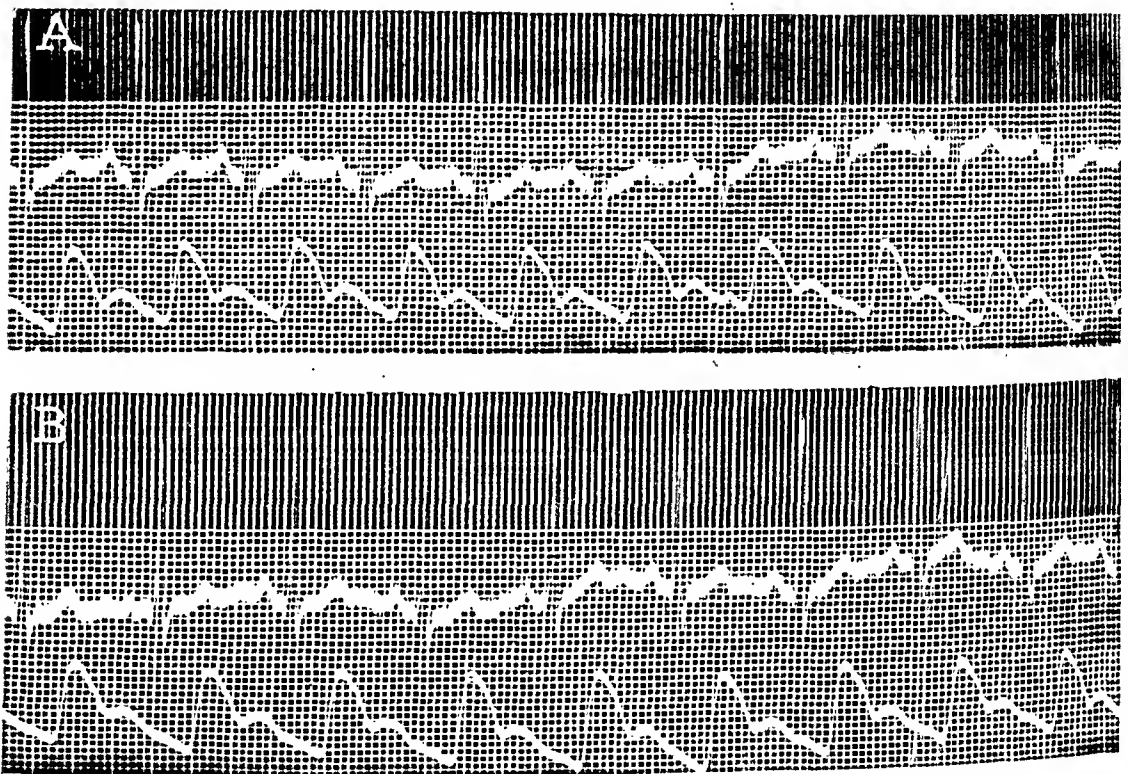


Fig. 5.

The dogs had never before received trichlorethylene, and consequently their electrocardiograms can be compared only with those obtained from the rabbits which had never before been anesthetized with the drug. If this is done, similarities are observed. The marked slowing and the presence of ectopic beats indicate an effect on the conducting mechanism of the dog's heart. The complete block shown in Fig. 4, as well as the

changes in the P wave, was probably caused by the comparatively larger amount of the drug employed in that experiment.

It is apparent that the administration of a therapeutic dose of trichlorethylene to normal human subjects or patients with cardiovascular disease does not produce significant electrocardiographic or blood pressure changes.

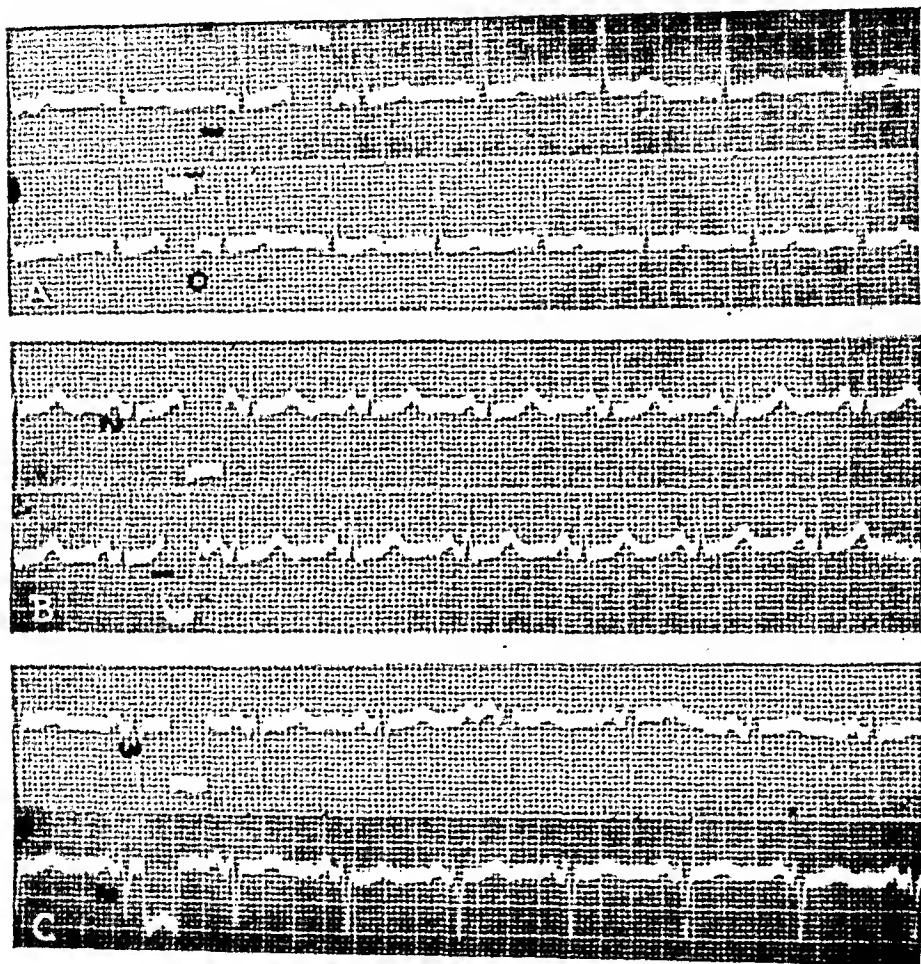


Fig. 6.

CONCLUSIONS

Studies were made of the effects of trichlorethylene on the electrocardiograms of human, canine, and rabbit subjects.

In the canine and rabbit experiments there were marked slowing of the heart rate, ectopic beats, and alterations in the P and T waves. The conducting mechanism and the myocardium were affected.

The administration of a therapeutic dose of trichlorethylene does not produce significant electrocardiographic or blood pressure changes in normal human subjects or in patients with cardiovascular disorders.

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TUMORS OF THE HEART

WITH A REPORT OF A PRIMARY FIBROMYXOSARCOMA OF THE LEFT AURICLE
AND THE PULMONARY VEIN, ASSOCIATED WITH MULTIPLE TUMORS
OF THE MESENTERY AND ALIMENTARY TRACT

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TUMORS of the heart are rare, and their recognition, particularly in the primary form, is exceedingly difficult. They are usually recorded as post-mortem curiosities and, up to the present time, the correct diagnosis has been made in only twenty cases.¹

The following case is unusual because the diagnosis was made during life and the tumor was found to be associated with other primary tumors.

REPORT OF CASE

A 57-year-old woman was admitted to the medical service of the Israel Zion Hospital Sept. 7, 1941. She stated that she had had "asthma" for twenty years, but gave no history of heart disease, hypertension, or rheumatic fever. She had undergone an appendectomy at 23 years of age, uterine myomectomy at 41 years of age, and cholecystectomy at 45 years of age. She was admitted to the surgical service of this hospital June 14, 1941, for "intestinal obstruction." This was relieved by conservative treatment, and she was discharged July 3, 1941. During her stay in the hospital, she had several attacks of fainting, accompanied by a thready pulse, and, at times, by paroxysms of auricular fibrillation. The electrocardiogram was normal, except for digitalis effect. She was readmitted to the surgical service Aug. 8, 1941, and a large encapsulated tumor was excised. This proved to be a cystic fibromyxosarcoma, apparently arising from the mesentery (vide infra). Histologically, it appeared to be of relatively low-grade malignancy, but of such a type that local recurrence could be expected. The patient made an uneventful recovery and was discharged Aug. 23, 1941. Her fourth and final admission to the hospital was on Sept. 9, 1941. She complained at this time of weakness, increasing cough, wheezing, and dyspnea, accompanied by choking sensations and a sense of precordial heaviness—all of five days' duration.

On admission she had pulmonary edema and auricular fibrillation, both of which disappeared within a few hours. On the following day she could lie flat on her back without dyspnea, and appeared somewhat pale. The heart was not enlarged and the action was regular; the rate was 84. The apex beat was snappy; the pulmonic second sound was louder than the aortic second. There were no murmurs. The neck veins were not distended. The right radial pulse was absent. The blood pressure was 150/80. There were dullness and a moderate number of subcrepitant râles at both bases posteriorly. Slight pretibial edema was also present. The liver and spleen were not enlarged. The admission diagnosis was "anemia, and acute left ventricular failure caused by myocardial disease."

Course.—During the following seventeen days, the patient had several transient attacks of syncope, auricular fibrillation, pulmonary edema, and increasing dyspnea, alternating with periods of comparative well-being. In spite of vigorous treat-

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ment with digitalis and mercurials, she developed increasing pretibial edema and pleural effusion. Except for occasional paroxysms of auricular fibrillation, the electrocardiogram was not remarkable. The circulation time was slightly prolonged (to 18 seconds). These clinical manifestations were definitely indicative of heart failure; nevertheless, it was pointed out that there was no specific evidence of any known cardiac disease to account for them. Therefore, in view of the fact that she was known to have had an abdominal neoplasm, the possibility that tumor invasion of the heart was responsible for the symptoms was now considered.



Fig. 1.—Mesenteric tumor, external view. A segment of the intestine can be seen adhering to its mid-portion.

Three days later, a most interesting observation was made. The dyspnea, which was not very noticeable while the patient was reclining, became so intensified when she was placed in the sitting position that she seemed to be choking. Relief occurred only when the patient was again placed flat on her back. The postural change in this symptom was now explained by assuming that she had a pedunculated heart tumor which produced a ball-valve obstruction of the mitral or tricuspid orifice when she was in the upright position. Her condition became progressively worse, and, on the following day, three weeks after admission, she died.

Her temperature ranged between 98 and 99.6° F. The electrocardiogram on September 8 showed a digitalis effect; on September 13, auricular fibrillation; and, on September 24, regular sinus rhythm and P_1 high, and P_2 notched.

Roentgenograms on September 16 showed "shady bases"; on September 26, "fluid in lung bases." The bones and lungs were free from metastasis.

The urine showed traces of albumin, an occasional erythrocyte, a few leucocytes, and casts; the specific gravity was 1.007 to 1.026. The hemoglobin was 50 to 63 per cent; the erythrocyte count, 3,600,000; and the leucocyte count, 6,000 to 11,400, with a normal differential. The blood glucose was 90 to 112 mg. per 100 c.c.; the urea nitrogen, 20 to 25 mg.; and the cholesterol, 240 mg.

Pathologic observations.—The abdominal tumor, which was removed surgically two months before death (Fig. 1), was a huge, football-sized mass weighing 2,070 grams and measuring 23 by 30 by 10 cm. A segment of small intestine was tightly adherent to it and had to be resected with it. The surface was lined by an intact, fibrous capsule, beneath which many semitranslucent cysts were bulging. On cross section (Fig. 2), it was honeycombed with numerous pea- to plum-sized cystic cavities, filled with amber- to ruby-colored serous and semigelatinous myxomatoid fluid which coagulated soon after exposure to the air. The inner lining of the cysts was smooth. The intervening connective tissue stroma was tough but relatively scant in amount.

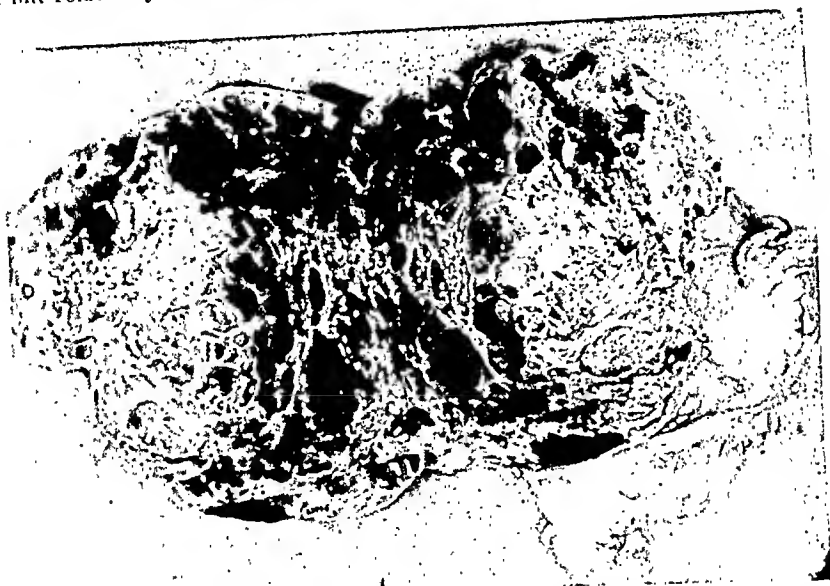


Fig. 2.—Mesenteric tumor, cross section. Note the numerous cysts, in some of which the semitranslucent myxomatous fluid can still be recognized. The thick, viscous, mucoid fluid, which oozed out from the tumor upon sectioning it, can be seen in the background.

Microscopically (Figs. 3 and 4), there was a variety of structures, consisting, in the main, of loose cellular connective tissue. The cells were, for the most part, rather large, pyramidal, stellate, or multipolar, and quite loosely distributed throughout the fine fibrillar stroma. The nuclei usually occupied the wider pole, varied in size, and were ovoid, rounded, or slender and oblong. The chromatin was arranged in fine specks, with occasional nucleoli and a well-defined nuclear membrane. Some of the cells were more sausage-shaped or stellate. The cytoplasm of the cells was abundant and deeply acidophilic; it ended in one wide, rounded process, and one, or several, pointed processes which were given off usually from the end farthest from the nucleus and merged with the intricate network of the matrix. Occasional nuclear hyperchromatism and mitoses were seen. The loose fibrillar and hyaline matrix was frequently divided into innumerable minute, refractile droplets, or bacilloid rods. This was especially seen in the vicinity of, and within, the cavities. Throughout the section there were many cystic cavities of various dimensions, filled with acidophilic granular debris, with

a scant number of mesenchymal cells interspersed. The lining of these cystic cavities was, for the most part, ill defined; their cells were identical and merged with the tumor cells. In places, however, distinct endothelium lined these cysts.

The relative proportion of the cells to the matrix varied. For the most part, the latter predominated; it was a rather loosely knit, fine, fibrillar meshwork which, in places, was pale staining, and myxomatous in appearance. Islands of cartilage cells and osteoid tissue, as well as bone trabeculae, were also seen here and there.

A mucicarmine stain showed a few scattered pinkish patches.

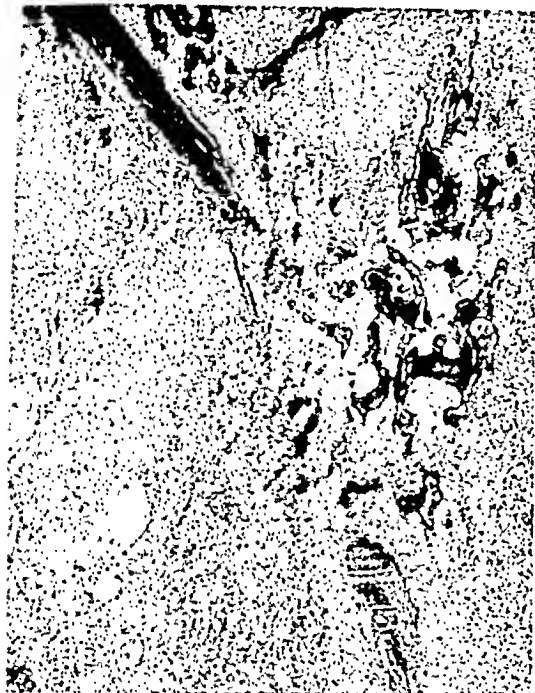


Fig. 3.

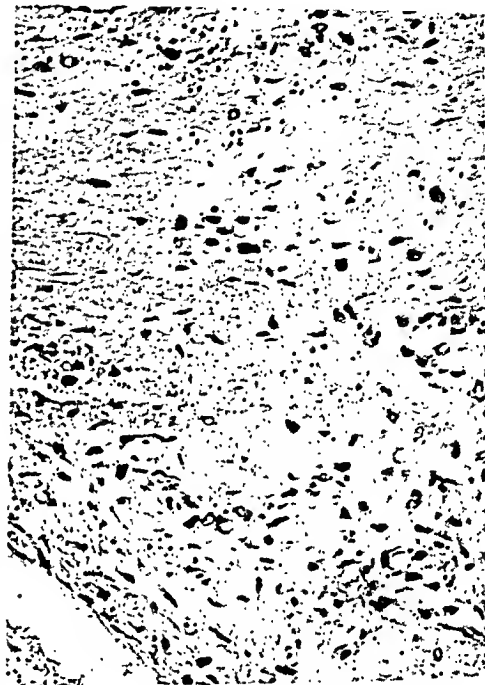


Fig. 4.

Fig. 3.—Low-power photomicrograph of mesenteric tumor, showing patches of myxomatous areas, varying in cellularity, with a number of giant nuclei in the lower half of the field. Five cysts are seen at the lower field. On the right are a number of bone trabeculae with islands of osteoid tissue and cartilage cells. (X25)

Fig. 4.—High-power photomicrograph of one field in Fig. 3, showing pleomorphism of cells and their nuclei. A cystic area is seen at the left lower corner. (X215)

Autopsy (two and one-half hours post mortem).—The body was that of a well-developed, obese, white female of the age of 65 years. The mucous membranes were moderately cyanosed. The abdominal and thoracic organs were in their natural position. The left and right pleural cavities contained 1,200 and 500 c.c. of serohemorrhagic fluid, respectively.

The heart (Figs. 5, 6, and 7) weighed 500 grams and measured 11 by 12 by 4 cm. There was a marked widening in the region of the left auricle, which bulged both anteriorly and posteriorly.

On opening, three polypoid tumor masses were found in the left auricle. The largest and the most anteriorly situated mass was the size of a tangerine, measuring 6.8 by 6.5 by 4 cm. It was situated mainly in the apex of the atrium, arising from its superior aspect. Its anterior and posterior surfaces were flattened, smooth, glistening, pale whitish, and lobulated. The free edge was tongue-shaped and beveled. The attached edge had a broad base 60 mm. in length, which merged imperceptibly with the endocardium. On section, it was hard and woody in some places and semielastic and rubbery in others. The second nodule was the size of a peach. It measured 50 by 30 by 10-20 mm. Its tongue-like free

edge was situated posteriorly to the larger mass, reaching a point 10 mm. from the origin of the third mass. At its right border it extended directly into the upper right pulmonary vein and occluded it completely (Fig. 7). A fresh, friable thrombus, 15 mm. in length, was adherent to the distal end of this nodule within the pulmonary vein. No break in the auricle or vein could be found. The lower branch of the right pulmonary vein contained no tumor, but was compressed externally by the tumor within the adjacent vein and auricle.



Fig. 5.—Heart, with the auricle, ventricle, and mitral valve exposed. The polypoid tumor can be seen filling the greatly dilated auricle. One tumor nodule extends just beyond the mitral valve.

The third mass was situated in the lowermost portion of the auricle. It measured 50 by 35 by 30 mm. It was attached by a broad base to the endocardium of the interauricular septum near the fossa ovalis, at a point 30 mm. proximal to the free edge of the posterior leaflet of the mitral valve. The foramen ovale was closed. When the heart was held vertically, the largest tumor reached the mitral valve, while the medium-sized tumor entered the mitral ring and spread apart its leaflets. The third tumor extended 15 mm. beyond the free border of the mitral valve, and lay on top of the apices of the papillary muscles.

The mitral valve was widened, measuring 9 cm. in circumference. Its posterior leaflet was slightly thickened, but otherwise it was normal. The left ventricle was small, about 30 mm. in depth. The left auricle was three times its normal size, measuring 11 cm. in its widest diameter, whereas the left ventricle was only 60 mm. wide in its widest portion. The wall of the left ventricle measured 25 mm., and that of the left auricle, 5 to 8 mm., in thickness. The aortic valve



Fig. 6.—Auricular tumor, resting upon the mitral valve, close-up view. In the upper left there is a cross section of one of the nodules, which shows the characteristic glazy or semitranslucent appearance of the tumor.



Fig. 7.—Heart, posterior view, showing the markedly dilated left auricle and the invading tumor within the right pulmonary veins.

measured 65 mm. in circumference, and its leaflets showed slight lipoidosis. The right auricle was somewhat dilated. The tricuspid valve measured 10 cm., and the pulmonary valve, 6 cm., in circumference. The wall of the right ventricle was somewhat thickened, measuring 10 to 15 mm. in width.

The aorta showed moderate subintimal lipoidosis. The left lung was atelectatic in places.

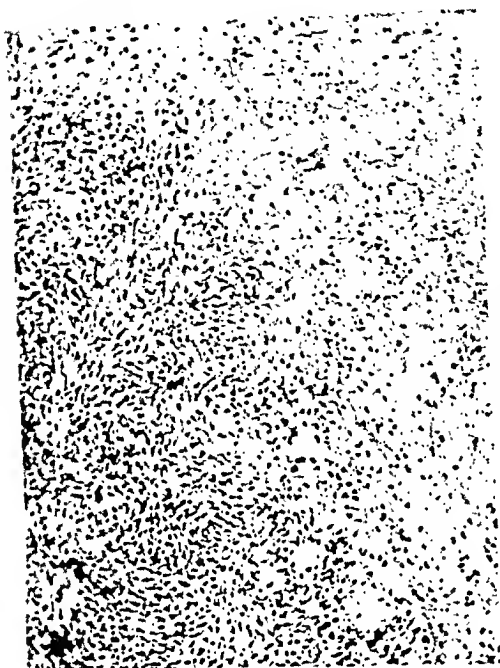


Fig. 8.

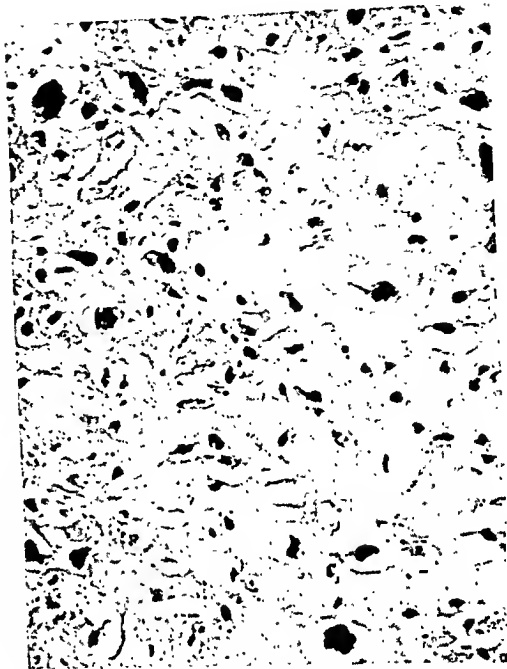


Fig. 9.

Fig. 8.—Medium-power photomicrograph of heart tumor, showing great variation in the histologic picture. The right half is more myxomatous and relatively acellular. The left half is more cellular and fibrous. In the left lower quadrant are seen a number of cells with bizarre shaped and giant nuclei. ($\times 95$)

Fig. 9.—High-power photomicrograph of heart tumor, showing the pleomorphism and two mitotic figures in the upper and lower edges. ($\times 250$)

Microscopically (Figs. 8, 9, and 10), the auricular tumor was composed of connective tissue cells arranged in whorls of all sizes, as well as in loose aggregates of no distinct pattern. There was great pleomorphism of the cells and their nuclei. The nuclei were rounded, oval, oblong, sausage-shaped, plump, or slender, and many of them were of a bizarre shape. Almost all the cells had one rounded end and another pointed one ending in one or several acidophilic processes which merged with the intricate network of the collagenous fibrils and the denser fibers of the matrix. A number of bi- or multinucleated cells were also found. The stroma varied in the amount of fibrillar elements; it was deep pink in some areas and loose, pale or faintly staining and myxomatous in others. The relative proportion of cells to stroma varied considerably in different fields.

Within the glazy myxomatous matrix, stellate and comma-shaped cells were seen. Islands of osteoid tissue, cartilage as well as bone, were also found.

The various histologic elements were more clearly brought out in differential stains with Van Gieson, Schmorl, and Mallory's phosphatungstic acid hematoxylin. With nunclearmine, only occasional pinkish areas were found.

The tumor blended imperceptibly with the subendocardial connective tissue layer of the atrium, but nowhere did it invade the myocardium.

In the pulmonary vein (Fig. 11), the tumor obliterated the lumen. The endothelium, however, was more or less intact. The tumor was of the same type as that in the auricle. At the edge of the advancing tumor there was a recent thrombus which showed beginning organization.



Fig. 10.—High-power view of another field of the auricular tumor, showing an almost acellular area, with myxomatous cells and matrix, and with one bone trabecula at the bottom. ($\times 200$)

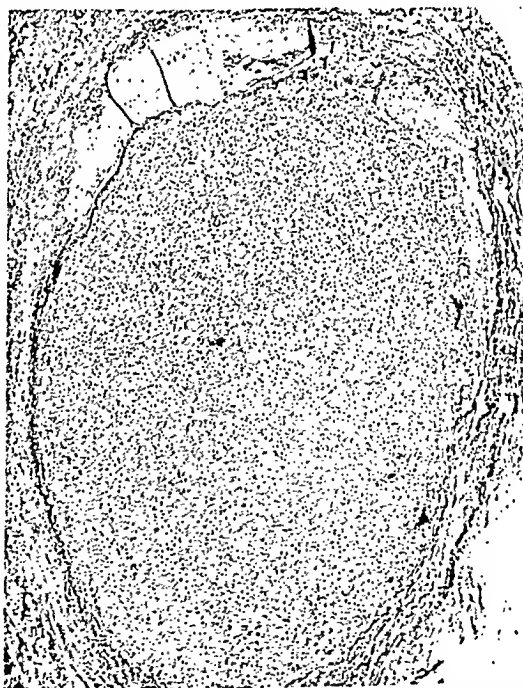


Fig. 11.—Low-power photomicrograph of the pulmonary vein occluded by the tumor. The uniform myxomatous character is more pronounced here. In the upper right corner a fresh hyaline thrombus is seen adhering to the tumor. ($\times 25$)

The stomach showed a small diverticulum along the lesser curvature and three pea-sized submucous polyps 2 to 5 mm. in diameter. Microscopically, the latter were made up of bundles of smooth muscle fibers in whorly arrangement, originating from the muscularis and replacing its upper layer.

In the jejunum there was a small mucosal nodule 12 mm. in diameter. Microscopically, it consisted of a miliary submucous nodule composed of whorls of spindle-shaped cells, with large hyperchromatic nuclei. This nodule was ill defined, more invasive, and occupied the mucosa as well as part of the submucosa.

In the rectum there was a cherry-pit-sized nodule 7 mm. in diameter, which, histologically, was an argentaffin or carcinoid tumor such as is not uncommonly found in the intestine and especially in the appendix.

In the uterus multiple leiomyofibromata were found.

The changes in other organs were insignificant.

The Anatomic Diagnoses were primary polypoid fibromyxosarcoma of the left auricle, with direct extension into the right upper pulmonary vein and secondary thrombosis of this vein; pulmonary edema; chronic passive congestion of the liver and spleen; diverticulum of the stomach; multiple submucous leiomyomata of the stomach; miliary submucous leiomyosarcoma of the jejunum; small argentaffin tumor of the rectum; multiple leiomyofibromata of the uterus; encapsulated, cystic, telangiectatic fibromyxosarcoma of the mesentery; and operative enteroanastomosis of the ileum.

COMMENT

The early symptoms in this case were indicative of left ventricular failure; yet no definite cardiac disorder could be discovered to account for it adequately. There was no cardiac enlargement or evidence of disease of the valves, endocardium, myocardium, pericardium, or coronary arteries. This disturbing inconsistency was stressed repeatedly, and therefore, on September 26, nineteen days after admission, it was postulated that the symptoms could be explained by a tumor of the heart, secondary to the pre-existing abdominal neoplasm. Four days later, because of the severe choking sensation induced by the sitting posture, a more definite diagnosis of ball-valve ostial growth was made, which was verified by autopsy. In this way the clinical manifestations could be readily explained. The dyspnea was caused by pulmonary engorgement resulting from obstruction of the blood flow through the pulmonary vein, left auricle, and mitral orifice. The outstanding single feature that led to the diagnosis of ball-valve tumor was the choking sensation produced by the upright posture, which, in turn, caused a more complete occlusion of the mitral orifice. In the reclining position the pedunculated masses were dislodged, with consequent resumption of the circulation. Incomplete mitral obstruction by the tumor accounted for the remainder of the symptoms, which consisted of transient attacks of pulmonary edema, fainting spells, feeble pulse, auricular fibrillation, and the meager evidences of mitral obstruction. The electrocardiogram, except for transient auricular fibrillation and high P waves, was not significant.

Relation of the Heart Tumor to the Mesenteric Tumor.—From the gross appearance alone, it was evident that there could be no direct connection between these two tumors.

The site of origin of each was in common with the usual locations of these respective types of tumor, and by no stretch of imagination could either be conceived of as a metastatic growth of the other. Histologically, however, it must be admitted that there seemed to be a great resemblance between the two, but this relationship was more apparent than real, i.e., it was at best only a generic one, for both were mesoblastic in origin.

Further support for the view that they were independent can be adduced from the fact that there were five other uncommon submucosal tumors: the leiomyomata of the stomach and intestines and argentaffinoma of the rectum, which surely bore no relationship to them. Thus, if there is such a thing as a "tumor diathesis," this patient presents a classical illustration of the phenomenon.

As to the pathogenetic relationship of this or any other myxomatous heart tumor to a thrombus—a view which has been in vogue and cited from time to time since the days of Czapek² and Thorel³⁻⁶—it is mentioned here only to be dismissed. For all the arguments in opposition to such a view which were advanced by Fawcett and Ward⁷ and others can, in the light of the above gross and microscopic observations, be applied with equal force in our case as well. It must be concluded, therefore, that these polypoid myxomatous tumors are true and genuine primary neoplasms, and bear no relationship whatsoever to a thrombus. A more plausible view is the one expounded by Ribbert,¹⁰ in 1904, namely, that they arise from isolated rests of embryonal myxomatous tissue along the valves and the endocardium, especially in the vicinity of the foramen ovale. This view can also be applied to the genesis of the large mesenteric tumor in our case.

DISCUSSION AND REVIEW OF LITERATURE

The incidence of tumors of the heart is extremely low. Thorel,³ in his comprehensive treatise "Pathologie der Kreislauforgane," in 1903, stated that he had not seen a single case of genuine primary tumor of the heart among 3,000 autopsies in Nürnberg within the period from 1894 to 1902. Nevertheless, case reports of such tumors have been appearing in the literature for the last one hundred years. The ratio of primary to secondary growths is given as 1:16. Scott and Garvin⁸ found 118 heart tumors among 11,100 consecutive autopsies in which 1,082 general tumors were encountered. Lymburner⁹ reported 52 heart tumors in 8,500 autopsies from the Mayo Clinic. Out of 40,000 autopsies, Benjamin¹⁰ reported 0.03 per cent of primary tumors and 0.5 per cent of secondary cardiac neoplasms. In a statistical study of the autopsy material at the Israel Zion Hospital, we have found an incidence of 0.05 per cent for primary tumors of the heart (one in 1,888

consecutive necropsies). Lisa, et al.,¹¹ recorded 119 cases which were reported in the literature from 1918 to 1941. In this group there were forty-one primary malignant tumors, 90 per cent of which were sarcomas, and forty-seven secondary malignancies, consisting of 50 per cent carcinomas and 25 per cent sarcomas. In this collection, there were thirteen cases which resembled ours in that there was a pedunculated mass in the left auricle which projected into the left ventricle through the mitral orifice.

From a review of the gross and microscopic appearance of the primary tumors of the heart which have been reported to date, it would appear that by far the most common type is the myxoma or the fibromyxosarcoma. Thus, most of the tumors which have been variously regarded as "polypoid fibroma," "spindle cell" sarcoma, giant cell sarcoma, "mixed cell" sarcoma, and simple "sarcomas" appear to belong to this type. It should be recognized that these tumors belong to one specific type, which is almost as distinct as that of fibromyoma of the uterus. All of them exhibit an almost stereotyped characteristic gross appearance and origin, and their histologic pictures are also frequently quite similar. As an example, we may cite our own case, which is almost identical with the one reported by Baumeister in 1906.^{12*}

The sites and methods of invasion of the various tumors are given as follows:¹³ In general, any portion of the heart may be involved; primary tumors involve the left side of the heart more frequently. They often arise from the fossa ovalis in the left auricle, forming a pedunculated mass which projects into the left ventricle through the mitral orifice and produces a ball-valve effect. Metastatic tumors occur more often in the right side of the heart, and the primary lesion may be situated in any organ of the body. Carcinoma of the breast and bronchus account for 48 per cent of cardiac metastases. The pericardium is usually invaded by mesothelioma and granuloma, the myocardium, by sarcoma, fibrosarcoma, and rhabdomyoma, and the endocardium, by myxoma and polypoid fibroma. There are three methods of spread of secondary tumors: (a) direct invasion, or extension from adjacent organs, as from the bronchi, lungs, mediastinum, or pleura; (b) infiltration by systemic diseases, as in Hodgkin's disease, leucemia, or sarcoid; (c) lymphogenous or hematogenous invasion from other organs, such as the breast, bronchi, or thyroid, and from the gastrointestinal, genitourinary, and biliary tracts.

The clinical manifestations are variable, and depend upon the size and location of the tumors. Pericardial involvement is suggested by

*Haythorn, Ray and Wolff,¹² quoting Thorel,¹³ state that Baumeister "seemed to have been the first to postulate that the tumors (fibromyxomas) began as organizing thrombi and underwent metaplasia into true neoplastic growths." Baumeister's original article, however, does not contain such a statement. On the contrary, Baumeister believed that his tumor was a genuine myxoma and "of congenital origin." Thorel,¹³ on the other hand, although Baumeister's tumor "showed histologically a typical myxomatous structure," doubted whether it was a myxoma, and thought that it was "an edematous ball thrombus" because it was not "subjected to the specific stain for mucus."

a friction rub, tamponade, or sanguinous effusion causing progressive cardiac enlargement, and fluoroscopic examination may reveal a rigid, nonpulsating cardiac border because of tumor infiltration. The electrocardiogram may show the R-T segment changes which are characteristic of pericarditis.

Myocardial invasion may be manifested by congestive failure, various arrhythmias, heart block, or auricular fibrillation. Encroachment on the coronary arteries will usually cause coronary insufficiency, with consequent myocardial anoxia, followed by angina and characteristic R-T-T changes.

Endocardial tumors can produce embolism, or bizarre murmurs if the valves are affected, or intermittent occlusion of the cardiac orifices. In a considerable number of instances, a pedunculated tumor interfered with the cardiac dynamics. If it projects into the mitral ostium, as it did in our case, it causes retardation and narrowing of the blood stream, producing signs of mitral stenosis. As the tumor continues to grow, it may produce a ball-valve mitral syndrome which consists of mitral stenosis, transient changes in the pulse and peripheral circulation, paroxysmal auricular fibrillation, and a variability of symptoms with postural changes (Abramson¹⁵). Moderate mitral obstruction may cause fainting and accentuation of dyspnea which are relieved by a change in the posture of the patient. More complete mitral obstruction may be responsible for peripheral circulatory disturbances which are characterized by "cadaveric coldness of all four extremities and the tip of the nose, sometimes proceeding to ischemic gangrene, and associated with intense cyanosis and with feeble or absent pulse" (Fishberg¹⁶). Sudden death occurs in 29 per cent of these cases.

The possibility of a cardiac tumor is hardly ever entertained, but with the additional knowledge derived from an ever-increasing literature on the subject, the condition should be more often considered. Metastatic tumor of the heart was first diagnosed by Roesler,¹⁷ in 1924, and ten years later the first correct diagnosis of primary tumor of the heart was made in this country by Barnes, Beaver, and Snell.¹⁸ The recognition of a primary heart tumor is extremely difficult, but the presence of a secondary tumor should be suspected when unexplained cardiac abnormalities develop after or during the course of neoplastic disease elsewhere in the body. The absence of any known types of heart disease to account for the presenting cardiac manifestations is very suggestive. Mitral stenosis of unknown cause occurs in 50 per cent of the cases, and, when accompanied by unexplained dyspnea and fainting spells which are influenced by postural changes, it offers an important diagnostic feature. The dyspnea is often unyielding and wholly out of proportion to the cardiac abnormalities. It may be a prominent symptom and it often occurs without orthopnea, which is unlike that of ordinary types of heart failure. Signs of ball-valve effects on the cardiac orifices, with or without postural changes, are also highly significant.

The sudden onset of transient arrhythmia or intractable heart failure, after known malignancy, is of valuable aid. Other helpful signs consist of bizarre, contradictory combinations, such as severe dyspnea without obvious cause which remains refractory to treatment, or mitral stenosis accompanied by peripheral circulatory disturbances. The electrocardiogram is not characteristic, but the transient nature of the various arrhythmias may be significant. Of more valuable aid in the diagnosis is the development of recurrent, unexplained, hemorrhagic pericardial effusion, or progressive, bizarre cardiac enlargement. Fluoroscopic examination may reveal rigidity of heart border, with absence of pulsation, as a result of tumorous infiltration of the epicardium. Positive evidence of the existence of a cardiac neoplasm consists, however, in the recovery of tumor cells, either from aspirated pericardial fluid or from a metastatic focus.

SUMMARY

A case of a primary cardiac tumor, in which the diagnosis was made during life and confirmed by autopsy, is presented. It was associated with multiple primary tumors in other organs. The pathogenesis, clinical manifestations, and diagnostic features of neoplasms of the heart are discussed.

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THE SIGNIFICANCE OF VASCULAR HYPERREACTION AS MEASURED BY THE COLD-PRESSOR TEST

OBSERVATIONS ON 200 NORMAL SUBJECTS OVER THE AGE OF 40

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ACCORDING to Hines and Brown,¹ essential hypertension is a syndrome which develops upon the soil of a hyperreactive vasomotor system. Subjects with vascular hypertonicity and normal blood pressure are regarded by the authors as candidates for the disease. In support of this view, Hines² has found a high incidence of hypertensive cardiovascular disease in the families of normal subjects who exhibit a hyperreactive response to the cold-pressor test. The fate of the hyperreactor, according to the author,³ is reflected by the observation that 38 per cent of twenty-one originally normal hyperreactors developed hypertension within six years, as compared to none of the normal hyporeactors. In line with this apparent trend is the author's statement that the incidence of hyperreaction in children approximates the combined incidence of hyperreaction and hypertension among adults.

Although most authors have reported data in accord with this concept, the observations of Pickering and Kissin⁴ did not confirm the view that a relatively high rise of blood pressure in response to a cold stimulus is peculiar to persons with potential or established hypertension. They noted that nine normal subjects with an average age of 53 years showed an average response similar to that of twelve hypertensive patients with an average age of 54 years. The small number of cases studied, however, does not permit acceptance of the authors' conclusions. The investigations of Chesley and Chesley,⁵ and Feldt and Wenstrand,⁶ on the other hand, seriously open to question the significance of a hyperreactive response in the development of essential hypertension. These authors, in studies on a large number of cases, found no relationship between the response to the cold-pressor test and a family history of hypertensive cardiovascular disease.

Further contradiction of the theory that hyperreaction indicates a predisposition to essential hypertension seems apparent from the original observations of Hines and Brown. They noted, paradoxically, that in the subjects with normal blood pressure there was an appreciable increase in the range of reaction in the latter decades of life. This is not in harmony with the authors' statement that "the response of the blood pressure is characteristic for the individual and probably remains so throughout life." Furthermore, calculations from the data in their tables would show that 35 per cent of normal subjects over the

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age of 40 years are hyperreactors, as compared to only 23 per cent under that age. Obviously, if hyperresponse in youth means hypertension later in life, one should expect to find a decreasing incidence of normal hyperreactors with increasing age. Yates and Wood⁷ did not find this to be the case, but their series included only thirty-four subjects over the age of 40 years, and thirteen of 50 years or older. They did not, however, observe a greater response in older subjects than in young ones, as reported by Pickering and Kissin.

Hines and Brown⁸ have attributed the increased incidence of normal hyperreactors among the older subjects of their series to a latent or subclinical form of essential hypertension. A study of fifty such persons between the ages of 34 and 65 years revealed no previous history of elevated blood pressure, although a hypertensive sclerosis of the retinal arterioles of Grade I or more was found in all instances. Some of their subjects who were followed for years did not show evidence of an elevated blood pressure. Nevertheless, a family history of hypertensive cardiovascular disease was found in 82 per cent of these hyperreactors, as compared with only 14 per cent of a group of hyporeactors. From the various studies of these authors, therefore, it would seem that hyperresponse at any age is associated with a positive family history in over 80 per cent of the cases. The present paper will attempt to show that this view is untenable for older persons, as indicated by clinical and statistical considerations.

The following series of observations on two hundred normal male subjects over the age of 40 years is being presented because it fails to support the idea that "vascular hyperreactivity" is a significant factor in the development of essential hypertension.

TECHNIQUE OF THE COLD-PRESSOR TEST

The procedure as outlined by Hines and Brown was followed throughout. The subject remained recumbent in a quiet room, and blood pressure readings were taken over variable periods until a basal level was reached. The rest period was twenty to thirty minutes, and, usually, four to five readings were made. The sphygmomanometer cuff remained on the arm during the whole procedure, and, when the lowest level of blood pressure was reached, the free hand was placed in a basin of water at a temperature of 4° C. The hand was kept immersed to a level just above the wrist for sixty seconds. The blood pressure was measured at thirty and sixty seconds.

The response is recorded as the difference between the basal level and the maximum reading. Using the authors' criteria, subjects whose response exceeded 20 mm., systolic, and 15 mm., diastolic, were called hyperreactors. Those whose response did not exceed these figures were designated as hyporeactors.

SUBJECTS OF TEST AND RESULTS

The test was performed on two hundred merchant seamen with normal blood pressure. All were ambulant hospital patients who had been admitted for a variety of minor ailments unrelated to the cardiovascular system. The blood pressure was not accepted as normal unless all

previous readings were below 145 mm., systolic, and 95 mm., diastolic. Many of the subjects knew approximately what their pressure was because of former recordings made prior to boarding ships. An appreciable percentage of them had had one or more previous admissions to this hospital over a period of years, and the available data served as an additional check on the accepted levels of pressure. The ages ranged from 40 to 69 years, and the average was 56 years. The results are summarized in Table I. The average response to the cold-pressor test was 21.4 mm., systolic, and 15.0 mm., diastolic. There were 82 hyperreactors (41 per cent), with an average response of 32.0 mm., systolic, and 21.5 mm., diastolic. Among 118 hyporeactors (59 per cent) the average response was 14.0 mm., systolic, and 10.4 mm., diastolic.

TABLE I
SUMMARY OF RESULTS WITH COLD-PRESSOR TEST

	SUBJECTS		AVERAGE RISE OF BLOOD PRESSURE IN MILLIMETERS OF MERCURY	
	NUMBER	PERCENTAGE	SYSTOLIC	DIASTOLIC
Entire Group	200	100	21.4	15.0
Hyperreactors	82	41	32.0	21.5
Hyporeactors	118	59	14.0	10.4

TABLE II
AGE AND AVERAGE RESPONSE TO THE COLD-PRESSOR TEST

AGE (YEARS)	ENTIRE AGE GROUP		HYPOREACTORS		HYPERREACTORS	
	SYSTOLIC RISE	DIASTOLIC RISE	SYSTOLIC RISE	DIASTOLIC RISE	SYSTOLIC RISE	DIASTOLIC RISE
40-49	14.0	10.0	10.6	7.5	24.6	18.0
50-59	22.6	16.6	15.0	11.8	33.0	23.3
60-69	27.6	18.1	17.5	13.2	35.5	21.9

Table II shows the effect of age upon the response to the cold-pressor test. For the entire group the average systolic elevation rose from 14 mm. in the fifth decade to 27.6 mm. in the seventh decade. The average diastolic response increased from 10.0 mm. to 18.1 mm. in the same interval. Among the hyporeactors the average systolic response increased from 10.6 mm. to 17.5 mm., whereas the average diastolic response increased from 7.5 mm. to 13.2 mm. in the age groups studied. In the hyperreactor group the average systolic response increased from 24.6 mm. in the fifth decade to 35.5 mm. in the seventh decade. The average diastolic response, on the other hand, increased from 18.0 mm. to 23.5 mm., and then showed a fall to 21.9 mm. with succeeding decades.

Chart I shows the effect of age upon the incidence of hyperreaction to the cold-pressor test. Of sixty-two subjects between the ages of 40 and 49 years, 24.2 per cent were hyperreactors. There were eighty-one subjects between the ages of 50 and 59 years, and, of these, 43.2 per

cent were hyperreactors. Between the ages of 60 and 69 years, 56.1 per cent of fifty-seven subjects showed hyperreaction to the cold-pressor test.

TABLE III

COMPARISON OF FAMILY HISTORY OF HYPERREACTORS AND HYPOREACTORS

SUBJECTS	NUMBER	POSITIVE FAMILY HISTORY OF HYPERTENSIVE CARDIOVASCULAR DISEASE	
		NUMBER	PER CENT
Entire Group	200	53	26.5
Hyperreactors	82	23	28.0
Hyporeactors	118	30	25.4

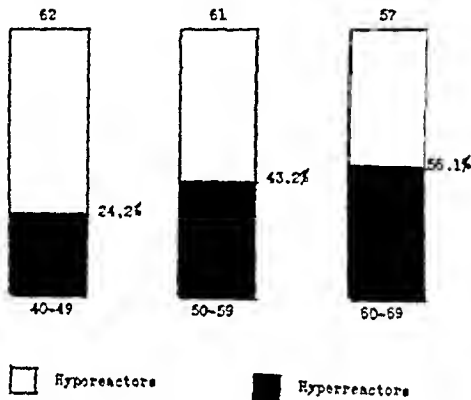


Chart I.—Age and hyperreaction to the cold-pressor test.

In eliciting the family histories, the same standards were applied in all instances, regardless of the cold-pressor response. The state of health, if living, and the cause of death, if deceased, of each parent and each sibling were noted. The subjects were specifically asked if their parents, brothers, or sisters were known to have, or to have had, elevated blood pressure, heart disease, or apoplexy. Only the instances of hypertension or of diseases considered to be the result of hypertension were accepted. Doubtful cases were not included in the study, but their addition would not alter the results because the proportion among hyporeactors and hyperreactors was relatively the same. Table III shows that the response to the cold-pressor test was not related to the family history in this series. Fifty-three subjects, or 26.5 per cent of the entire group, gave a family history of one or more instances of hypertensive cardiovascular disease when parents and siblings were counted. Twenty-three (28.0 per cent) hyperreactors and thirty (25.4 per cent) hyporeactors had such a family history. These figures are greatly at variance with those of Hines, but are in close agreement with the observations of Feldt and Wenstrand.

DISCUSSION

The concept advanced by Hines and Brown assumes that: (1) the cold-pressor response is characteristic for the individual throughout

life, and (2) hyperresponse to the test indicates a predisposition to essential hypertension. If these hypotheses are true, static studies of various age groups should reveal: (1) a decrease in the incidence of normal hyperreactors with advancing age, and (2) an incidence of hyperresponse in children which approximates the combined incidence of hyperresponse and hypertension in adults. Neither of these, however, has been established. The present study indicates a rise in the incidence of hyperresponse from 24.2 per cent in the fifth decade to 56.1 per cent in the seventh decade. The tables of Hines and Brown reveal (by inference) a similar trend with age; 23 per cent were hyperreactors under the age of 40 years, whereas 35 per cent showed a hyperreactive response over that age. The observations of Feldt and Wenstrand were of the same order. Available data, therefore, indicate an appreciable rise, rather than the anticipated fall, in the incidence of hyperresponse with advancing age.

Secondly, since Hines⁹ found that 18 per cent of school children are hyperreactors, it is to be expected that the combined incidence of hyperreaction and hypertension in adults will approximate this figure. A study of the levels of blood pressure among aged seamen¹⁰ revealed, for the age group 60 to 69 years, that 60 per cent had normal pressure, 19 per cent had diastolic hypertension, and the remainder were arteriosclerotic subjects with systolic hypertension. Since 56.1 per cent of the normals in the present study were hyperreactors, the latter would represent 33.7 per cent of this age group comprising all levels of blood pressure. In other words, if we assume that arteriosclerotic persons are all hyporeactors, as reported by Hines and Brown, then, in these subjects between the ages of 60 to 69 years, there would be 33.7 per cent normal hyperreactors and 19 per cent hypertensives. The combined incidence would be 52.7 per cent, a figure almost three times the incidence of hyperreaction in the school children previously mentioned. The fact that many of these elderly hyperreactors may be subclinical hypertensives, as alleged by Hines, would not alter the situation, for the combined incidence would still be unchanged. Although the racial and environmental factors in the school children differ from those in the seamen, it is felt that this source of error cannot materially affect the final deductions.

These observations, therefore, seem to offer serious contradiction to the original assumptions of Hines and Brown. Furthermore, inasmuch as the combined incidence of hyperresponse and hypertension in old age far exceeds that of hyperresponse in childhood, the conclusions of Hines regarding family history do not seem valid. This author has stated that "a positive family history of hypertensive cardiovascular disease is 4 to 5 times as frequent among individuals who have hypertension or who are hyperreactors to a standard stimulus test, than it is among individuals who react normally to the test." Since the author noted a positive family history as frequently among elderly hyper-

reactors as among young ones, it would have to be concluded that, in advanced age, a greater percentage of persons belong to hypertensive families than in childhood—a deduction which is contrary to clinical and statistical experience. The present study on subjects over the age of 40 years, furthermore, has shown no relationship between the nature of the cold-pressor response and the family history of hypertensive cardiovascular disease.

The cause of the rising incidence of hyperresponse in successively older groups seems apparent from a consideration of Table II. It is seen that there is not only an increase in the average response of hyperreactors with advancing years, but also an appreciable rise in the average response of hyporeactors. Consequently, it would appear that a hyporeactor at 40 years might become a hyperreactor at 60 years. Since immersion of the hand in ice water for one minute actually produces pain, it seems likely that the older subject will respond with a greater rise in pressure than the younger one whose threshold for pain and vasomotor stability are undoubtedly greater. These data are at variance with those of Hines, who found no significant change in the range of reaction in hyporeactors with advancing years.

Because of the supposed specificity of hyperresponse with respect to hypertension, the use of the cold-pressor test has been advocated as a diagnostic aid in the recognition of latent hypertension.^{11, 12} It has been stated that a hyperresponse to the test in the presence of cardiac failure and normal blood pressure is evidence of previous hypertension which is temporarily latent. When it is realized that perhaps 45 to 50 per cent of normal subjects over the age of 50 years show a hyperreactive response to this test, its limitations as a diagnostic method in older persons seem evident.

Although the significance of vascular hyperreaction cannot be fully evaluated until further time has elapsed, the results of this study appear to indicate that hyperresponse in normal, middle-aged, and elderly subjects is unrelated to hypertension.

CONCLUSIONS

An analysis of the cold-pressor response in two hundred normal male subjects between the ages of 40 and 69 years revealed that:

1. Forty-one per cent of the entire group were hyperreactors to the stimulus of cold.
2. The incidence of hyperresponse, contrary to theory, increased, with advancing age, from 24.2 per cent in the 40- to 49-year group, to 56.1 per cent in the 60- to 69-year group.
3. The average response of both hyporeactors and hyperreactors increased with age. Consequently, a hyporeactor at 40 years might become a hyperreactor at 60 years. The increased response was attributed to changes in the threshold for pain and increasing vasomotor lability with succeeding decades.

4. There is no support for the view that the cold-pressor response is characteristic for the individual throughout life.
5. The combined incidence of hyperresponse and hypertension in the subjects 60 to 69 years of age was almost three times the incidence of hyperresponse in the school children observed by Hines. The fact that elderly hyperreactors may actually be latent hypertensives would not influence this comparison.
6. There was no relationship between hyperresponse and a positive family history of hypertensive cardiovascular disease.
7. The high incidence of hyperresponse in normal subjects over the age of 50 renders the test unreliable in the diagnosis of latent hypertension, associated with congestive failure, in this group.
8. Hyperresponse among normal subjects in the later decades of life is unrelated to essential hypertension.

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Clinical Reports

STAPHYLOCOCCUS AUREUS SUBACUTE BACTERIAL ENDOCARDITIS SUPERIMPOSED ON A CONGENITAL HEART LESION, WITH RECOVERY

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THE usually fatal outcome of subacute bacterial endocarditis makes noteworthy all reports of recovery from this condition. A case is presented of subacute bacterial endocarditis due to a *Staphylococcus aureus* infection of a congenitally patent interventricular septum (Roger's disease); the patient was followed for four years after recovery.

CASE REPORT

Los Angeles County Hospital Permanent File No. 108-957. P.B., a single, 18-year-old white girl, was admitted to the hospital for the second time, Aug. 25, 1937, with the complaint of chills and fever of two weeks' duration. Pain in the lower part of the right hemithorax, aggravated by respiration, had also been noted for two days.

The past history was essentially negative, except that she was known to have had "heart trouble" since birth. The first hospital entry, at the age of 11, May 26, 1930, was for study of the heart, although the patient had no cardiac complaints. At this time it was noted that the patient had had heart disease since birth, and had not been expected to survive infancy. No definite information was obtained as to whether or not she had been a "blue baby." Physical examination at this time revealed a well-developed girl who weighed 67½ pounds and was 52½ inches tall. The heart was noted to be enlarged transversely. There was a harsh, blowing, systolic murmur which was heard best at the third left intercostal space, was transmitted along the left sternal border, and was associated with a marked systolic thrill. The fingers were clubbed. A diagnosis of congenital defect of the interventricular septum was made. The only illnesses which the patient had had were measles and mumps as a child. The system history gave no significant information. The family history was none contributory.

Physical Examination.—The patient was a well-developed young girl who was cyanotic and appeared acutely ill. Her temperature was 103.2° F.; her pulse rate, 116; her respiratory rate, 32; and her blood pressure, not recorded on entry, was later 115/80. The tonsils were moderately enlarged and the pharynx appeared slightly injected. A few small lymph nodes were palpable in the neck. The lungs showed dullness on percussion, with diminished breath sounds at the right base. A few moist râles were heard in this area and in the right axilla. The heart was enlarged, with the angle of cardiac dullness 1 to 2 cm. lateral to the left mid-

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clavicular line. The apex impulse was located in the fifth left intercostal space in the midclavicular line. A systolic thrill was palpable in the fourth intercostal space at the left sternal border. There was a harsh systolic murmur at the apex, obliterating the first sound. A systolic murmur was heard all over the precordium and in the left axilla. The liver and spleen were not felt. No masses were felt in the abdomen. There was slight clubbing of the fingers. The reflexes were normal. Pelvic and rectal examinations were not done.

Laboratory Examination.—(See Table I for routine laboratory studies and blood cultures, Fig. 2 for electrocardiograms, and Fig. 3 for chest roentgenograms.)

Progress and Treatment.—See Table II for details of treatment, and Fig. 1 for temperature curve correlated with treatment.

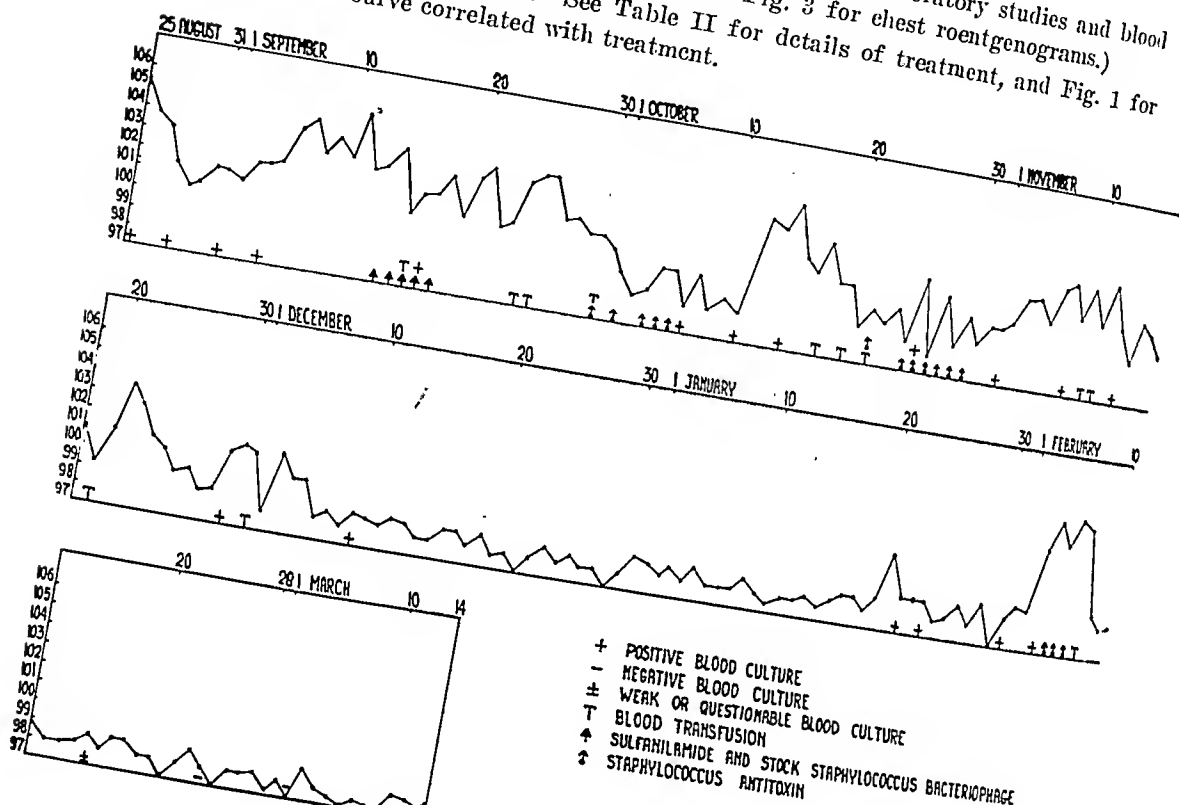


Fig. 1.

Course.—With the repeatedly positive blood cultures for *Staphylococcus aureus*, the cardiac abnormalities, and the febrile course, the diagnosis of staphylococcus endocarditis and a congenital septal defect appeared established. The illness divided itself into four periods:

1. Febrile period: Aug. 11, 1937, to Dec. 8, 1937. (Received two courses of staphylococcus antitoxin.)
2. Quiescent period, with normal temperature: Dec. 8, 1937, to Jan. 20, 1938. (No specific treatment.)
3. Two periods of fever: Jan. 20, 1938, to Feb. 8, 1938. (One course of staphylococcus antitoxin.)
4. Convalescent period, with normal temperature: Feb. 8, 1938, to July 7, 1938. (No specific treatment.)

During the first period, the patient had a high fever, appeared acutely ill at all times, and had repeated chills. Although no petechiae were noted on entry, definite petechiae were seen, a few days after entry, on the left hand and in the right conjunctiva. Jaundice was first noticed Sept. 10, 1937, before any therapy was

TABLE I
LABORATORY DATA

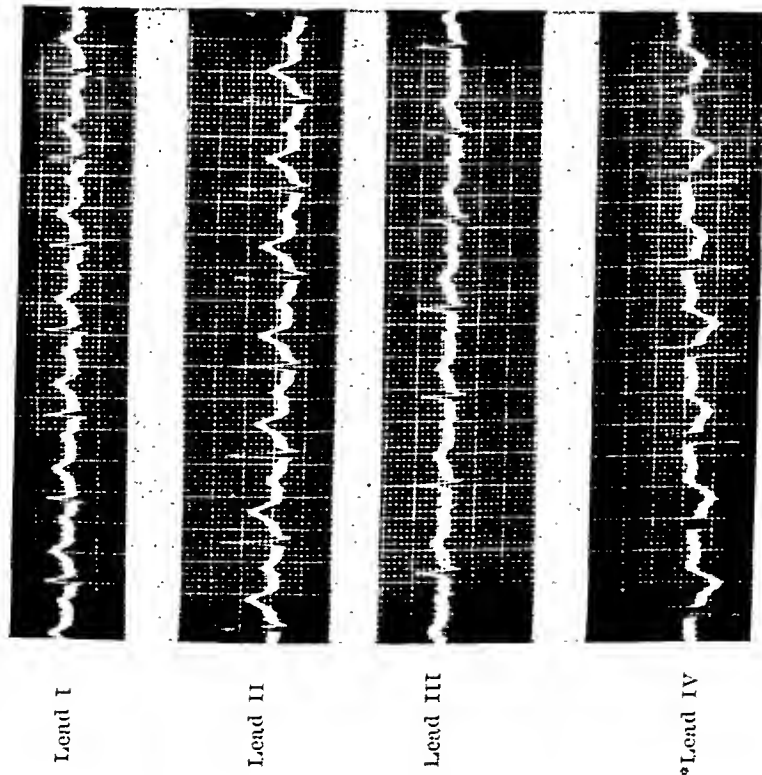
DATE	HGB. % (SAHL)	R.B.C. IN MIL- LIONS	W.B.C. IN THOU- SANDS	DIFF. COUNT	URINE	BLOOD CULTURES	MISCELLA- NEOUS
8/25/37 8/29/37	85	4.2	14.6	P 64	Negative	Positive cultures for <i>Staphylococcus</i> <i>aureus</i> on: 8/25/37; 8/28/37; 9/1/37; 9/4/37; 9/13/37; 10/7/37; 10/11/37; 10/14/37; 10/26/37; 11/2/37; 11/8/37; 11/13/37; 11/29/37; 12/9/37; 1/22/38; 1/24/38; 1/31/38; 2/3/38; 2/15/38; few staph. on direct smear from culture. No growth on sub- cultures	Widal and undulant fever ag- glutina- tions neg- ative Blood Was- sermann and Kahn negative Pleural fluid: no growth
9/ 9/37					No albumen. Micro- scopic: 1-2 W.B.C. per high field. Few R.B.C.; Rare casts		
9/13/37	80	4.3	14.2	P 72			Icterus in- dex 57.6.
9/21/37							Prompt
10/17/37	78	3.85					Van den
11/17/37	80	4.01	8.35	P 68			Bergh
12/ 1/37	85	4.87	16.4	P 68			4.5 mg. bilirubin
2/ 2/38	75	3.0	7.35			Negative cultures on: 2/24/38; 3/3/38; 3/11/38; 3/16/38; 3/26/38; 3/29/38 4/1/38, plate: 1 colony of <i>Staph.</i> <i>aureus</i> ; broth: no growth 4/11/38, negative 4/25/38, doubtful, gram-negative bacillus 5/2/38, negative 5/16/38, 1 colony of staph. in 1 c.c. plate culture. 6/22/38, negative. 7/22/38, diphtheroid bacillus 8/19/38, negative	Sedimenta- tion rate 12 mm./hr.
2/10/38	84	3.5	7.3	P 50			
4/ 7/38	13.6 grams	4.01	6.4	P 59			

started. By September 21, the icterus index was 57.6 units. The jaundice had disappeared by Nov. 17, 1937. When positive blood cultures for the *Staphylococcus aureus* were obtained, an attempt was made, without success, to obtain a specific bacteriophage. A stock staphylococcus bacteriophage and sulfanilamide were tried, without any effect on the clinical appearance or the temperature. Staphylococcus antitoxin (Lederle) was then tried in conjunction with repeated, small blood transfusions. With practically every dose of antitoxin the patient had chills, and on several occasions developed urticaria and joint pains. Many of the transfusions of citrated blood were also accompanied by chills. There appeared to be improvement after the antitoxin, although fever recurred and the blood cultures remained positive.

In the second period, Dec. 8, 1937, to Jan. 20, 1938, the patient appeared slightly improved. No definite embolic phenomena were noted, although the blood cultures remained positive.

Fig. 2.
Electrocardiograms

Aug. 25, 1937



*Lead IV in this tracing old precordial lead—right arm electrode on apex, and left leg electrode on left leg. All other Fourth Leads are IV F type.

March 13, 1938

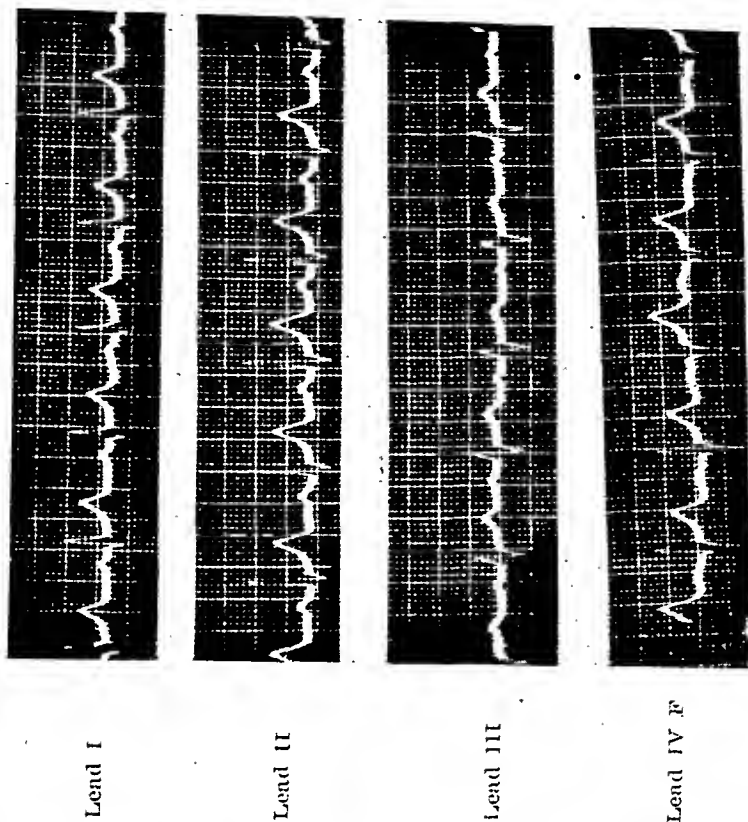
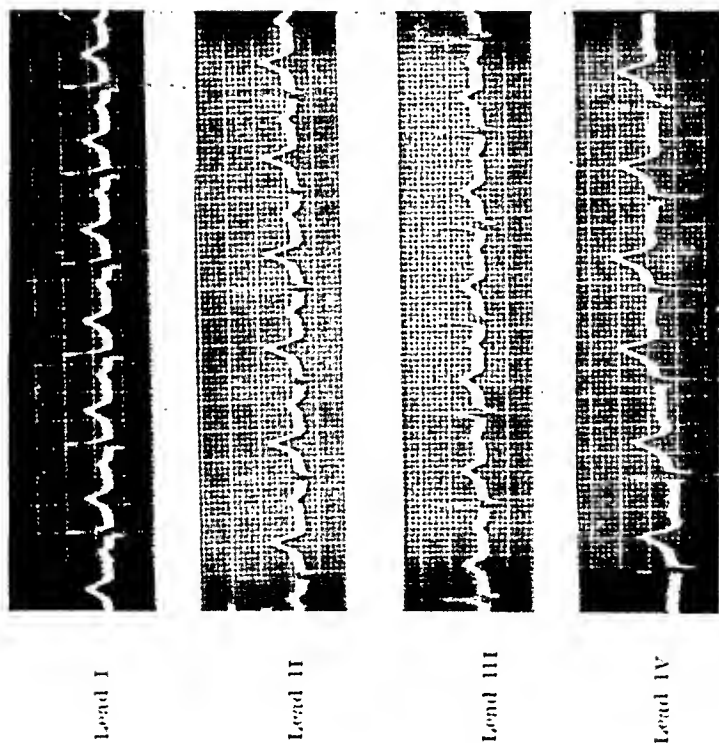


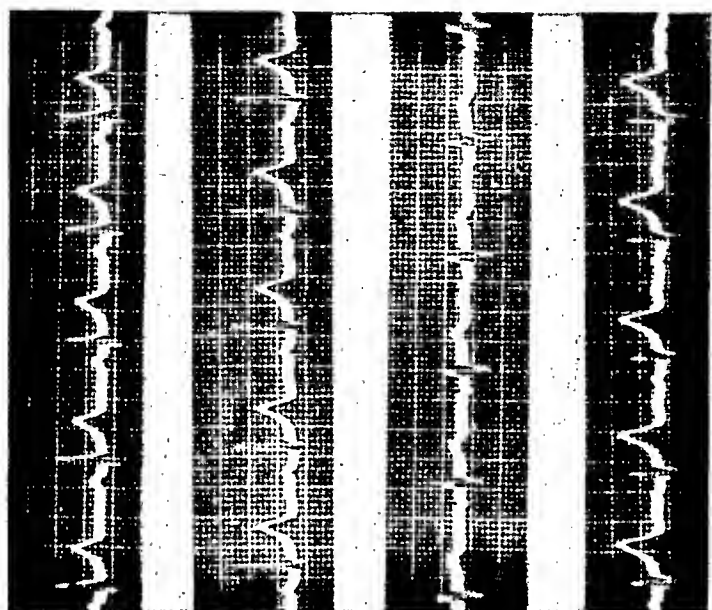
FIG. 2.—Cont'd
Electrocardiograms

June 21, 1938



Heart rate — 92/min.
Slight sinus arrhythmia.
P-R interval — 0.17.
Well-defined Q wave — Lead I.
Some slurring of QRS in Leads I and III.
No significant T-wave changes.

AUG. 7, 1938

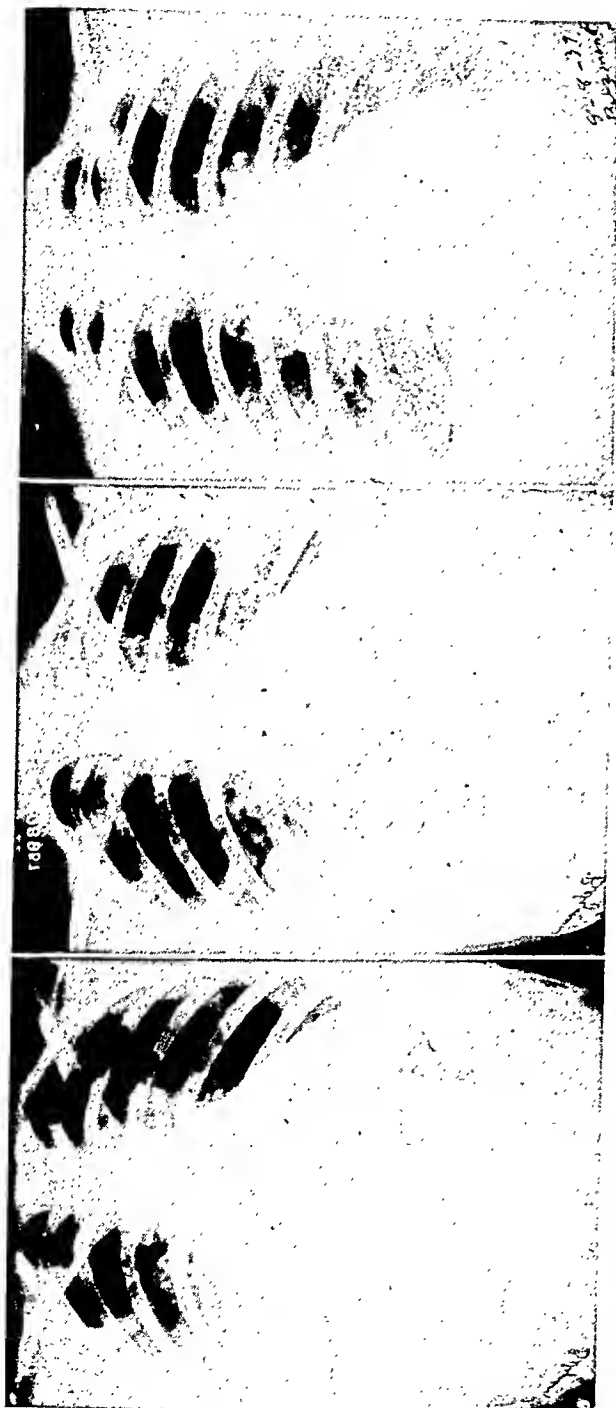


Heart rate — 80/min.
Sinus arrhythmia.
P-R interval — 0.2 second.
QRS interval — 0.06 second.
Left axis deviation.
QRS small and slurred in Leads I and III.
Prominent Q in Lead I. T upright in standard leads; large in Leads I and II. Rr is depressed. Low voltage QRS Lead IV F. T wave in Lead IV F upright and large.

Fig. 3.
Chest Roentgenograms
Sept. 22, 1937

Aug. 26, 1937

Aug. 8, 1939



Heart definitely enlarged to about twice its normal size, with a mitral form. The left costophrenic sulcus is not clearly seen, apparently because of a small pleural fluid collection. The right base is filled with hazy, homogeneous density which is apparently parenchymal in location and may represent a pneumonitis surrounding a septic embolus. Because of the absence of the costophrenic sulcus, at least part of the abnormal density must be assumed to be caused by a pleural fluid collection.

Since examination of Aug. 26, 1937, there has been marked decrease in the density at the right base. However, there is still some hazy opacity in this region and, in addition, a localized zone of hazy density in the left midlung field and at the left base.

Orthocardiogram: Cardiac silhouette bulbous and at upper limits of normal in size. There has been definite decrease in the left-sided enlargement of the cardiac silhouette since Sept. 22, 1937. Fluoroscopically, pulsations appeared forceful and of normal rate and rhythm. Aorta slender. The infiltrative lesion at the right base has entirely disappeared, only some coarsening of bronchovascular detail remaining in this region. The opacity throughout the left lung has also disappeared. Several strandlike densities remain at the left base, with slight obliteration of the costophrenic sulcus. These have the appearance of old adhesions. Lung fields are now otherwise essentially clear.

TABLE II
SUMMARY OF TREATMENT

DATE	BLOOD TRANS- FUSIONS (CITRATED BLOOD)	STOCK STAPHY- LOCOCCUS BACTERI- OPHAGE	SULFAN- ILAM- IDE	STAPHYLOCOCCUS ANTITOXIN
9/15/37	400 c.c.—(chill)	1 c.c. intra- venously	40 grains by mouth	
9/14/37	? amount given	1 c.c. intra- venously	80 grains by mouth	
9/15/37		1 c.c. intra- venously	60 grains by mouth	
9/16/37			60 grains by mouth	
9/17/37			60 grains by mouth	
9/24/37	350 c.c.		60 grains by mouth	
9/25/37	200 c.c.			5,000 units intramuscularly
10/ 1/37	200 c.c.			20,000 units intravenously—(chill)
10/ 2/37				15,000 units intravenously—(chill)
10/ 4/37				20,000 units intravenously—(chill)
10/ 5/37				30,000 units intravenously—(chill)
10/ 6/37				
10/18/37	200 c.c.			
10/20/37	250 c.c.			
10/22/37	150 c.c.			Small amount (? amount)
10/25/37				20,000 units intravenously—(chill)
10/26/37				20,000 units intravenously—(chill)
10/27/37				40,000 units intravenously—(chill and urticaria)
10/28/37				20,000 units intravenously
10/29/37				20,000 units intravenously
10/30/37				20,000 units intravenously
11/10/37	250 c.c.			
11/11/37	200 c.c.—(chill)			
11/19/37	350 c.c.			
12/ 1/37	Part of trans- fusion with severe reac- tion			
2/ 4/38				20,000 units intravenously, with cevitamic acid, in divided doses after careful desensiti- zation—(urticaria)
2/ 5/37				10,000 units intravenously with cevitamic acid—(severe reaction)
2/ 6/38				10,000 units intravenously with cevitamic acid—(urticaria, joint effusion, laryngeal edema, precordial pain)
2/ 7/38	300 c.c.—severe reaction			

In the third period, from Jan. 21, 1938, to Feb. 8, 1938, there were two periods of fever: a mild one on January 21, and a severe one starting on February 3, with a chill and temperature of 104° F. At this time, a third course of staphylococcus antitoxin was given, with severe reaction (chills, urticaria, joint effusions, and laryngeal edema), despite careful desensitization.

After the last elevation of temperature, on Feb. 8, 1938, the patient slowly improved, although there were questionable petechiae on March 30, and a questionably positive blood culture in May, 1938. She was discharged from the hospital July 6, 1938, ten and one-half months after entry. At this time she had been up for one month in a wheel chair, with occasional walks around the ward. Her weight was 125 pounds. On entry her weight was 130 pounds, with a low point, four months after entry, of 100 pounds (January, 1938).

She was followed in the outpatient clinic for three months after discharge from the hospital, and showed gain in weight and strength. Because she left Los Angeles, frequent examinations were impossible. However, the patient has kept us informed by letter, about every six months, as to her condition, and has returned to the hospital for examination about once a year. In April, 1941, the cardiac murmur and thrill were unchanged. The last report by letter, December, 1941, states that she is leading an entirely normal life and has no cardiac symptoms.

DISCUSSION

Libman,^{1,2} Hamman,³ Weiss and Rhoads,⁴ and others have commented on the occurrence of healed bacterial endocarditis (of the *Streptococcus viridans* group), clinically and pathologically. It is their experience that, in mild cases, the disease frequently goes undiagnosed, and the patient may recover, and that, in severe cases, the patient may recover and have a later recurrence. Some of the clinical reports of recovery appear doubtful because of possible diagnostic errors and too short periods of observation. The chronicity of the disease requires a period of observation of one and one-half to three years before one can be sure that recovery has occurred. The problem in treatment of typical subacute bacterial endocarditis caused by the *Streptococcus viridans*, however, appears quite distinct and different from the situation encountered in this patient.

No previous reports of recovery from subacute bacterial endocarditis caused by the *Staphylococcus aureus*, with or without treatment with staphylococcus antitoxin, have been found in the literature. The case presented here fulfills the majority of the points for diagnosis of subacute bacterial endocarditis and for recovery from this condition:

1. Known heart lesion seven years prior to the onset of the febrile illness.
2. Positive blood cultures for six months.
3. Evidence of embolic phenomena: petechiae and pulmonary infarcts.
4. Irregular, prolonged febrile illness.
5. Progressive, mild anemia.

Recovery was attested by: (1) negative blood cultures, (2) clinical improvement, and (3) observation for four years.

From the clinical aspect, several features of this case are of interest. No point of origin or entry of the staphylococcus was discovered.

Since small skin lesions may go unnoticed, this does not appear an unlikely possibility. The urine examination on entry excluded the kidneys as a possible focus. It is also of note that the spleen was never palpable, although repeated examinations of the abdomen were made. The finger nails developed very unusual, marked, transverse striations, corresponding chronologically to each separate febrile period.

From the therapeutic standpoint, the relationship of the staphylococcus antitoxin to the recovery is difficult to evaluate. It is a matter of experience that certain patients with acute staphylococcus septicemia recover, but this is rarer with chronic staphylococcus sepsis. Staphylococcus antitoxin was given to this patient because of the dramatic results obtained, at the same time, in a 14-year-old Mexican boy. This patient entered the hospital in an apparently moribund state, with staphylococcus sepsis, with pyemic abscesses in the skin, lungs, and kidneys, and with osteomyelitis. He was given 80,000 units of staphylococcus antitoxin (Lederle) daily for several weeks, with marked improvement within twenty-four hours, and final recovery. It was never possible to give the patient with the endocarditis the antitoxin in the recommended therapeutic dose because of severe reactions. Thus, she received only 90,000 units between October 1 and 6, 140,000 units between October 25 and 30, and 40,000 units between February 3 and 6. From the graphs of the temperature (Fig. 1), it is apparent that the first course of staphylococcus antitoxin was given at a time when the temperature curve was already falling, so that the effect on the temperature is not clear. The improvement in the clinical condition was definite, however. The second course of staphylococcus antitoxin was also given at a time when the temperature was normal. It is to be noted that, after stopping the antitoxin, in each of those instances, the temperature rose. The third and last course of staphylococcus antitoxin was followed by a marked and permanent lowering of the temperature to normal and by negative blood cultures. The severe reactions with practically every injection of antitoxin, as well as with many of the blood transfusions, may also have had a therapeutic effect through a "shock" action. Although no one who saw this patient felt positive about the effect of the staphylococcus antitoxin, the consensus was that it had been beneficial for the outlook before its use had appeared hopeless. The work of Tager⁵ on the relative value of staphylococcus antitoxin and the sulfonamide compounds in acute staphylococcus infections in mice is of interest in this connection. He reviews experimental and clinical results. From his own results he concludes that "a single early dose of antitoxin proved superior to sulfapyridine and sulfathiazole, but did not surpass the activity of sulfamethylthiazole." He believes a combination of antitoxin and sulfathiazole is superior to either agent alone. This he attributes to the possibility that the staphylococcus toxin is an important factor in the pathogenicity of the staphylococcus. The chemotherapeutic agents appear

not to be antitoxic. This work suggests that the best therapeutic results in staphylococcal sepsis would be attained by a combination of the antitoxin and one of the sulfonamide drugs.

SUMMARY

A case of subacute bacterial endocarditis caused by the *Staphylococcus aureus*, with recovery and a four-year period of observation, is reported. The possible beneficial effect of staphylococcus antitoxin in the treatment in this case is discussed.

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RARE CARDIAC ANEURYSM IN A CHILD

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J. HAMILTON CRAWFORD, M.D.
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THE final analysis of the unusual cardiac configuration found in a 13-year-old child, as previously reported in the *AMERICAN HEART JOURNAL* by Hollander and Crawford,¹ may now be presented with the aid of necropsy observations.

Since the recognition, in 1938, of this cardiac deformity in the child, she was followed in the cardiac clinic, but there was no apparent change in her physical condition. She was last seen in the clinic about six months before her death. Her mother states that the child had been well and active during this time. While at play in one of the city playgrounds, the child became ill and sat down to rest. She died within a short time, before any medical aid could be obtained.

POST-MORTEM EXAMINATION

Because of the sudden death, the post-mortem examination was performed by the Medical Examiner.² It revealed a well-nourished and well-developed, muscular child, measuring 155 cm. in length. There were no external evidences of injury. The essential abnormalities were limited to the heart. The pericardial sac contained a small quantity of clear, straw-colored fluid, and the serosal surfaces were everywhere smooth and glistening. No congenital abnormalities were found in the great vessels. A large, somewhat lobulated, sacular mass bulged from the lateral margin of the left ventricle (Fig. 1). It was completely covered by the visceral pericardium. A few firm, fibrous adhesions bound the superior surface of the aneurysmal sac to the parietal pericardium. Several fibrous adhesions traversed the shallow sulci formed by the superior and inferior lobules of the sac. The aneurysm measured 9 cm. between the superior and inferior surfaces, 6 cm. from the base of the mitral ring to the outermost border, and 6.5 cm. between the anterior and posterior borders of the sac. A sagittal section of the aneurysm (Fig. 2) revealed a lobulated, thin-walled sac in which there were partially formed ridges tending to divide the chamber into two or three incompletely formed compartments. The superior compartment contained a massive, laminated blood clot which was firmly adherent to the inner wall of the sac. The remaining compartments of the aneurysm were free from blood clots. The lining of the sac was smooth, white, and glistening. The thickness of the wall varied from 0.1 to 0.5 mm.; it consisted of white, glistening, connective tissue. The origin of the aneurysm was sharply limited to the fibrous connective tissue ring of the mitral valve, and did not involve the muscular wall of the left ventricle except for the posterior portion, which appeared fused by newly formed connective tissue and by the adipose tissue of the epicardium to the wall of the sac. The orifice of the sac was situated beneath the lateral leaflet of the mitral valve and was in direct communication with the chamber of the left ventricle. The greatest diameter of the opening measured 1.5 cm. A smooth, white, glistening, endocardial surface lined the wall of the orifice. The valve leaflet and

¹From the Departments of Pathology and Medicine, Long Island College of Medicine and Kings County Hospital.

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*The authors are indebted to Dr. M. E. Martin, Chief Medical Examiner, for the use of the necropsy material.

the cordae tendineae overlying the opening into the sac were not involved. The aneurysm did not distort the architecture of the heart, although the appendage of the left auricle was situated in a pocket formed by the superior pole of the sac and the base of the aorta and pulmonary artery. The heart valves were thin and delicate and showed no gross evidence of either active or healed rheumatic endocarditis. The chordae tendineae were thin and delicate and attached beyond

Fig. 1.



Fig. 2.

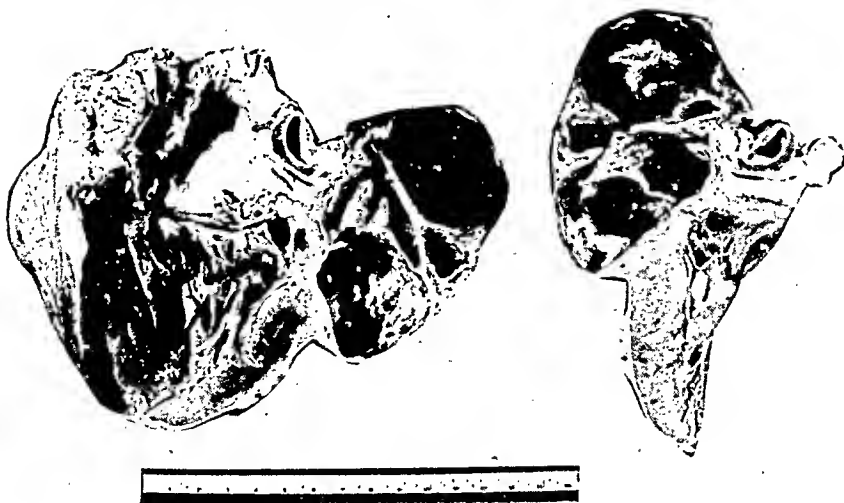


Fig. 1.—Posterior view of heart, with aneurysm arising from left ventricle.

Fig. 2.—Sagittal section of aneurysm, showing opening into left ventricle beneath the lateral leaflet of mitral valve.

the free edge of the valve leaflets. Sections of the myocardium were homogeneous, dull red, and without gross evidence of increased fibrosis. The heart was not hypertrophied nor dilated, but it weighed, together with the aneurysm, 550 grams. The coronary vessels were of the usual distribution. The outer surface of the aneurysm was partially supplied by small branches from the left coronary artery. The coronary vessels were thin walled and patent throughout.

Examination of the other viscera, including the brain, showed no significant changes except acute congestion of the spleen, liver, and lungs.

MICROSCOPIC EXAMINATION

Microscopic sections from a number of different locations of the aneurysmal wall revealed a compact, hyalinized, fibrous, connective tissue wall that was free from endothelial lining. Some of the sections contained either partially organized blood clots or firm, dense masses of fibrin and platelets. The outer wall of the aneurysm consisted of loosely arranged, collagen forming, connective tissue in which there were groups of young, spindle-shaped fibroblasts. Many greatly engorged and thick-walled arterioles were distributed throughout the external coat of the sac. Many of the vessels were surrounded by collars of cells composed primarily of large mononuclear cells, plasma cells, and lymphocytes. An occasional polymorphonuclear leucocyte and eosinophilic cell was observed in the cellular exudate. Some of these foci, particularly those situated near blood vessels, showed a tendency to form imperfectly shaped Aschoff bodies. The mononuclear cells found in these zones were large cells with basophilic cytoplasm containing one and occasionally two large vesicular nuclei which had a central dense clump of chromatin. The exudate not only surrounded the blood vessels, but was rather diffusely scattered throughout the edematous connective tissue in the areolar tissue surrounding the sac. Similar isolated groups of engorged blood vessels, with their collars of mononuclear and plasma cells, were seen in the dense, hyalinized connective tissue wall of the aneurysm. Isolated groups of newly formed lymphoid follicles were observed in some of the sections that were removed from near the base of the sac. Microscopic sections from the ring of the mitral valve, near the region of the orifice of the aneurysm, displayed a granulomatous and cellular tissue reaction that contained many young capillaries, fibroblasts, and an abundant, diffuse, cellular exudate characterized chiefly by large mononuclear cells, plasma cells, and lymphocytes. This granulomatous lesion apparently diffusely involved the entire mitral ring, and in some places extended for a short distance along the interstitial tissue of the mitral leaflet, but did not involve the endocardial surface. Throughout the myocardium of both the left and right ventricles there were many well-developed, typical Aschoff bodies comprised of the usual large mononuclear and binucleated cells, together with some plasma cells and lymphocytes. Some of the muscle fibers appeared small and atrophic. Many focal areas of myocardial fibrosis were observed in all of the sections of the myocardium. The coronary arteries and pericardial surfaces were free from involvement.

COMMENT

An intensive search of the literature revealed only three other reports of a cardiac aneurysm identical in anatomic structure with the one observed in this child. Hunter and Benson² described a ruptured sacular aneurysm in a 45-year-old adult who died suddenly. These same authors referred to the only other report in the literature that described a similar cardiac deformity. Corvisart,³ in 1797, described an aneurysm in a 27-year-old negro who also died suddenly, but without rupture of the sac. More recently Berlin and Hollén⁴ described a similar type of

aneurysm in a 39-year-old man. Aneurysms of the heart in children are extremely uncommon, as mentioned in the previous report.¹

Certain outstanding anatomic characteristics, common to all three of the aneurysms described, seem to distinguish these unusual cardiac deformities from the better known cardiac aneurysms which result from coronary occlusion. In each of the cases reported, the out-pouching developed on the lateral border of the left ventricle, and seemed to arise chiefly from the fibrous ring of the mitral valve. The opening into the aneurysm is small and is located inferior to the lateral leaflet of the valve. There is some tendency to lobulation of the sac and to development of incompletely formed chambers from poorly formed septa. No muscle fibers are present in the wall of the sac except for a few isolated strands that fuse into the base of the aneurysm from the left ventricle.

Unfortunately, a detailed history of the earlier period of the child's life is not available, so that the time of onset and progress of the development of this aneurysm are not known. Several of the anatomic features of the aneurysm suggest that it may have been a congenital development from the fibrous band of the mitral ring. On the other hand, the presence of both acute and chronic rheumatic lesions in the interstitial tissue points to an inflammatory reaction as a possible etiological factor. Certainly, coronary occlusion and syphilitic inflammatory reactions are eliminated as factors in the formation of this saccular aneurysm.

SUMMARY

The necropsy observations on an unusual and rare cardiac aneurysm in a child are reported. The anatomic characteristics of the structure suggest that it was a congenital abnormality arising from the fibrous band of the mitral ring.

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Correspondence

To the Editor:

In the paper by Wood, Wolferth, and Geckeler, entitled "Histologic Demonstration of Accessory Muscular Connections between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex," published in the *AMERICAN HEART JOURNAL*, April, 1943, p. 454, there appears parenthetically the categorical statement: "Kent was the first to describe the auriculoventricular bundle, although His' name has been applied to it," which I feel should not be permitted to pass unchallenged.

I have prepared a fully documented analysis of the relevant literature, but it is entirely too long for publication as "Correspondence." What follows is a brief summary of the cardinal points made in the full account, which I am attaching to this letter.

In 1892-1893, Kent searched for muscular tissue bridging the A-V junction in subhuman hearts. In one and the same heart he claims to have found it crossing the ring in various localities in the form of "nets," "hands," and "sheets." Yet he concluded this series of papers with the statement: "In a later paper I propose to deal with the exact location of the connection between auricles and ventricles. . . ." The illustrations consist of seven reproductions of histologic preparations. One is from the "junction of right auricle and ventricle;" the part of the junction supplying the other sections is not specified. In none can features characteristic of the A-V bundle be recognized.

In 1894, relative to the human heart, he speaks of "strands" of muscular tissue passing across the groove in unspecified locations, and, in addition, describes a mass muscular continuity, not at all resembling the A-V bundle, but in a situation which might have included the septum, although, if this mass contact included, or was in, the septum, that is not mentioned.

In a series of papers published during 1913-1914, Kent, without in the meanwhile having dealt "with the exact location of the connection," (1) states he has maintained since 1892 that "the muscular path of communication is undoubtedly multiple;" (2) deals specifically with "a muscular connection . . . at the right margin of the heart," which he says he "described in 1892 in lower animals and in 1893 in man" (I have not succeeded in finding specific mention of a connection in that location in the only paper by Kent [1894] that deals with the human heart); and (3) states that after severing "all of the structures which connect the auricles to the ventricles with the exception of a strip of

tissue on the right lateral aspect of the organ, spontaneous beats arising in the auricle still pass through to the ventricle and evoke ventricular beats," a result which, I say advisedly, never has been confirmed by any investigator.

Certainly no one could have surmised, on the basis of the above exhibit, that there is a particular muscular connection in the septal region of the A-V junction, or that functional integrity of a path there, is essential to the maintenance of the normal A-V sequence.

Now for the chronology of *the* A-V bundle. It is exactly identified, both descriptively and pictorially, in a number of mammals including man, by His, in a paper appearing in "*Arbeiten aus der medizinischen Klinik zu Leipzig*," the preface to which, dated March, 1893, states that the volume consists of "an account of research conducted during the last four years. . . ."

In 1895, His announced that section of only this one bundle produces lasting heart block, a result since abundantly confirmed; and, in 1899, he described the first case of heart block to be recognized in man. Here His thus summarizes correctly the situation relative to the question of muscular continuity across the layer of connective tissue in the A-V junction: "Muscle fibers," he says, "have been found in this layer (Kent) and I myself have demonstrated a bundle which is present both in mammals and in man, and runs from the posterior wall of the right auricle to the ventricular septum."

In conclusion, may I add that if, as Kent maintains, there is a right lateral muscular connection in all mammals (in addition to the many other connections he claims he has seen), it is obvious that it does not function as a path for A-V conduction under experimental conditions, Kent to the contrary notwithstanding. And if it is such a right lateral connection that is responsible for the rare clinical condition described by Wood, et al., one ponders the nature of the process that converts a connection which cannot, by experimental procedures, be made to conduct vicariously, into one which transmits impulses faster than the normal path. Is it not possible that short P-R intervals may be the result of a physiologic anomaly rather than an anatomic anomaly?

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Abstracts and Reviews

Selected Abstracts

Bond, D. D.: Sympathetic and Vagal Interaction in Emotional Responses of the Heart Rate. *Am. J. Physiol.* 138: 468, 1943.

Changes in heart rate of unanesthetized dogs and cats, startled by a short, unexpected noise, were recorded electrically. The cardiac responses from the animals when normal were compared to the responses from the same animals after various nerves had been cut.

Intact dogs and cats yielded a complex pattern of a sudden, high rise in heart rate, beginning immediately after the startle. This was successively followed by a sharp fall, more pronounced in dogs, a second rise of variable height, and, thereafter, several undulations in rate until a termination of the response in two to three minutes.

Adrenaline plays a more prominent role in cats than in dogs; but its action in either species appears only after twelve seconds.

Dogs in which the vagi and depressors were cut and adrenaline excluded showed pure accelerator activity. The response was similar to that of the normal in promptness and magnitude, but was simpler, with no secondary fall or further undulations.

In dogs and cats with the sympathetic cardio-accelerators removed, and with adrenaline excluded, startle was promptly followed by inhibition of vagal tone. Cats, in addition, showed an acceleration that was greater than could be accounted for by loss of vagal tonic influence alone. Unless there were a few rapid beats of vagal origin occurring in certain individuals immediately after the stimulus, no fall in rate subsequent to the initial rise was seen. If these rapid beats were present, they were commonly followed by one very slow beat only. This seems to indicate that usually the increase of heart rate did not raise arterial pressure to a degree sufficient to trip a depressor mechanism acting primarily through the vagus. Evidence is presented that the carotid sinus is involved.

The effect of respiration on cardiac rhythm is complex and may greatly affect the pattern of response. Apnea may cause a speeding of the heart or may be accompanied by a slowing.

The discussion deals with the quick activity of the sympathetics, the role of the vagus, and the relation of the responses reported here to those obtained by others from direct and reflex cardiac acceleration.

AUTHOR.

Hitchings, G. H., Daus, M. A., and Wearn, J. T.: Chemical Changes in the Rabbit Heart During Hypertrophy. *Am. J. Physiol.* 138: 527, 1943.

When aortic insufficiency is produced in the rabbit heart by rupturing an aortic valve leaflet, rapid changes occur in the chemical composition of the myocardium. During the first three days there is a transient increase of extracellular phase of considerable magnitude. The intracellular phase appears to hypertrophy at a more or less constant rate for several weeks, after which further increases cannot be clearly distinguished. The hypertrophied hearts at intermediate periods are characterized by a proportion of intracellular phase somewhat greater than normal, but of approximately normal composition, except for an increased intracellular water content. At later periods, a tendency for a loss of intracellular constituents is observed.

AUTHORS.

Rosenblueth, A., and Acheson, G. H.: The Influence of Interelectrode Distance in Electrical Stimulation of Nerve and of Striated and Ventricular Muscle. *Am. J. Physiol.* 138: 583, 1943.

With short distances between the stimulating electrodes, the threshold of C nerve fibers rises significantly, but not as much as does that of A fibers.

The threshold of striated and ventricular muscle to electrical stimuli is independent of the interelectrode distance. The threshold of striated muscle is also independent of the angle between the stimulating current and the muscle fibers.

AUTHORS.

Neumann, C.: A Study of the Effect of Spontaneous Variations in Blood Pressure Upon Spontaneous Variations in the Volume of the Finger Tip. *Am. J. Physiol.* 138: 618, 1943.

By the simultaneous use of a plethysmograph for recording changes in volume of the tip of the left index finger, and of an intra-arterial manometer for obtaining synchronous readings of the blood pressure of the left radial artery, it was shown that the spontaneous variations (increase or decrease) in volume of the finger tip are not concordant with spontaneous changes in blood pressure (? Traube-Hering waves), and are present even in the absence of measurable variations in blood pressure. A few exceptions were noticed. Rises in systemic blood pressure during expiration were accompanied by variable but small increases in volume of the finger tip. Marked lowering of blood pressure accompanying cardiac asystole was reflected in a decrease in volume. The rule then seems to be that variations in the volume of the finger tip usually go on independent of changes, or lack of change, in blood pressure, though under certain conditions there may be a transitory relationship. When present, it is manifested by an increase in volume when there is a rise in blood pressure.

AUTHOR.

Lewis, T.: Trousseau's Phenomenon in Tetany. *Clin. Sc.* 4: 361, 1942.

In a case of tetany, Trousseau's sign was easily elicited. It has been shown, in this case, that the spasmodic affection of the hand, on occluding the circulation to the arm, resulted from ischemia of the nerves under the cuff. The phenomena of irritation described by Trousseau, and those of paralysis where the nerves of the normal limb are deprived of circulation, are interestingly comparable, though the former are naturally much earlier manifestations.

AUTHOR.

Lewis, T.: Observations Upon the Vascular Axon Reflex in Human Skin, As Exhibited by a Case of Urticaria, With Remarks Upon the Nocifensor Nerve Hypothesis. *Clin. Sc.* 4: 365, 1942.

A case of urticaria, with occasional subcutaneous swellings, is described, in which a general skin eruption could be produced by applying heat to the lower limbs.

In addition, a constellation of urticarial wheals could be produced at, and around, the site of a quite local cutaneous stimulus, such as heat, freezing, severe pressure, or faradism; it could be reproduced around histamine punctures of the skin.

The constellation of wheals fell always within the area exhibiting the vascular flare, and, when sufficiently extensive, corresponded closely with the distribution of the latter.

As in the case of the flare, so this reaction was found to be dependent upon the functional integrity of cutaneous nerves, but to be independent of the central nervous

system. Flare and satellite wheal are regarded as produced through the same nervous mechanism, an axon reflex.

Because general whealing of this patient's skin could be induced by injecting pilocarpine subcutaneously, and local whealing, by ionizing either pilocarpine or an acetylcholine compound into the skin, and because the spontaneous eruption could be controlled by atropine, the nerves involved are regarded as cholinergic.

The occurrence of satellite wheals in the area of flare is evidence of H-substance release through the axon reflex. Such a release links the axon reflex effects with antidromic vasodilatation. In view of the work of Grant, Pearson, and Comeau, and of the present observations, both these effects are now regarded as produced by one and the same system of cholinergic nerves.

The abnormal factor in the patient was in the skin itself, this organ being rendered unusually responsive by some abnormal quality of the patient's blood plasma.

Between two hypotheses, that which supposes antidromic impulses and axon reflexes to make use of sensory (pain) nerve channels, and that which supposes them to make use of special (nocifensor) nerve channels belonging to the posterior root system, the balance of evidence appears still to favor the latter.

AUTHOR.

Cohen, H., and Jones, H. W.: The Reference of Cardiac Pain to a Phantom Left Arm. *Brit. Heart J.* 5: 67, 1943.

Two cases are recorded of cardiac pain referred to a phantom left arm.

Anesthetization of the brachial plexus of the phantom caused, in one case, abolition of the phantom component of the cardiac pain, and in the other, significant delay in the appearance of the phantom component, which led to a reversal of the site of onset and spread of cardiac pain.

AUTHORS.

Horvath, S. M., Dill, D. B., and Corwin, W.: Effects on Man of Severe Oxygen Lack. *Am. J. Physiol.* 138: 659, 1943.

Schizophrenic patients have been subjected to severe anoxia over a period of several minutes either up to the point of unconsciousness or in some cases extending into unconsciousness. The following conclusions are drawn:

Anoxia of severe degree produces no beneficial effects on the mental condition of this class of psychotic patients.

Anoxia severe enough to produce brief periods of unconsciousness has no lasting harmful effects on the central nervous system.

Respiratory stimulation by anoxia is strong and sustained even during unconsciousness.

Inferentially, circulatory function is also well sustained.

There is a remarkably rapid return to normal when either air or 14 per cent oxygen is supplied.

A mixture of 4.2 per cent oxygen with nitrogen is equivalent physiologically to an altitude of about 31,000 feet.

It should be possible to descend with an opened parachute from 31,000 feet altitude, without oxygen equipment, with no ill effects from anoxia.

AUTHORS.

Cossio, P., Berconsky, I., and Trimani, A.: The Formation of Auricular Diastolic Murmurs in Complete A-V Heart Block. *Rev. argent. de cardiol.* 9: 238, 1942.

The recording of the heart sounds in three cases of complete auriculoventricular block showed that the auricular sound was formed by two components of vibrations.

The first component was more marked at the beginning of the ventricular diastole, disappearing sometimes when auricular systole occurred at the end of the ventricular diastole. The second component did not change in intensity throughout diastole, or was more marked when it occurred toward the end of auricular systole.

These findings support the hypothesis that the vibrations of the first component of the auricular sound are due to distention of the ventricle, while those of the second component are due to elevation and tension of the auriculoventricular valves, once terminating auricular systole.

AUTHORS.

Bozler, E.: *The Initiation of Impulses in Cardiac Muscle*. *Am. J. Physiol.* 138: 273, 1943.

The action potentials of isolated cardiac muscle were recorded in an attempt to detect the processes which initiate the beats and which are responsible for the rhythmicity of heart action. Confirming earlier work on other muscles with automaticity, it was found that spontaneous impulses are initiated by weak local potentials, which are present in a large part of the muscular tissue, but which are strongest near the origin of the impulses. A phase of gradually rising negativity precedes each impulse in muscles with normal rhythmicity, but in injured muscles, there may be instead regular potential oscillations of gradually increasing magnitude. These oscillations give rise to the phenomenon of the Luciani periods if several waves in succession cause the discharge of impulses.

Each impulse is followed by an afterpotential which is normally positive, but which is oscillatory under certain abnormal conditions. The oscillations of the afterpotential may give rise to the discharge of further impulses like those of prepotentials. Acetylcholine diminishes the magnitude of the oscillations in the auricle and sinus venosus, but not in the ventricle; adrenaline increases their magnitude. None of the drugs alter their frequency.

It may be expected that a consideration of the local potentials will be helpful in the understanding of certain types of abnormal rhythmicity of the heart.

AUTHOR.

Hoff, H. E., Nahum, L. H., and Kaufman, W.: *Distribution in Leads I, II, and III of Potentials Applied to the Surface of the Heart*. *Am. J. Physiol.* 138: 644, 1943.

Potential differences applied across the surfaces of the right and left ventricles cause an upward deflection in the standard leads of the electrocardiogram when the negative electrode is on the right ventricle, and a downward deflection when the negative plate is on the left ventricle.

Potential differences applied across the centers of the anterior surface of the right ventricle and the posterior surface of the left ventricle affect preponderantly Lead III of the electrocardiogram. The projection in the horizontal plane of the line joining these centers is roughly parallel to the longitudinal axis of the body.

Potential differences applied across the centers of the anterior surface of the left ventricle and the posterior surface of the right ventricle are recorded preponderantly in Lead I. The projection in the horizontal plane of the line joining these centers is roughly parallel to the transverse axis of the body.

AUTHORS.

Langendorf, R., Hurwitz, M., and Katz, L. N.: *Electrocardiographic Patterns of Combined Ventricular Strain*. *Brit. Heart J.* 5: 27, 1943.

An analysis of forty-seven cases showing a combination of features of right and left ventricular strain in the cardiogram is presented. These were then cor-

related with clinical data and, in nineteen instances, with the available autopsy findings.

Six electrocardiographic patterns of combined ventricular strain are described.

The cardiographic diagnosis of combined ventricular strain was substantiated by clinical, radiologic, or post-mortem evidence in 81 per cent of the cases.

In a control group of twenty-nine autopsied cases of bilateral ventricular hypertrophy, in the absence of myocardial infarction, acute cor pulmonale, intraventricular block, or digitalis effect in the cardiogram, cardiographic evidence of combined strain was present in 27.5 per cent. In 35 per cent of the same series, no ventricular preponderance and no axis deviation, or only normal right or left axis shift, were present; this substantiates the statement that absence of ventricular preponderance in the cardiogram, in the presence of clinical or radiologic evidence of cardiac enlargement, is presumptive evidence of combined ventricular strain.

Other factors like displacement of the heart, congenital anomaly of the conduction system, or focal intraventricular block may be responsible for a pattern suggestive of combined ventricular strain.

Further anatomical correlation studies are necessary to establish the diagnostic accuracy of the cardiographic patterns of combined ventricular strain.

AUTHORS.

Williams, C., and Ellis, L. B.: Ventricular Tachycardia: An Analysis of Thirty-Six Cases. *Arch. Int. Med.* 71: 137, 1943.

An analysis is reported of thirty-six cases of paroxysmal ventricular tachycardia. In twenty-four, the electrocardiograms showed the attack to be uninterrupted, and in twelve the attacks occurred in short runs of tachycardia interposed between periods of normal supraventricular conduction. These two types have been arbitrarily designated as "persistent" and "intermittent" tachycardia.

In all but one case, organic heart disease was present; in twenty-eight cases it was of the degenerative type.

Digitalis intoxication was clearly associated with the attack in eight instances and was the probable precipitating factor in nine more. One patient had received large doses of both digitalis and quinidine prior to the onset of the attack. Attacks occurred in association with myocardial infarction six times, and in three instances, myocardial infarction was probably present.

Twenty-one patients died in the hospital, eight in the attack, and twelve (all but one of the remainder) within a month of its cessation.

The occurrence and prognosis of the attacks have also been analyzed in respect to associated electrocardiographic abnormalities and such factors as age, heart rate, and width of QRS. The prognosis of paroxysmal ventricular tachycardia is serious, but it is essentially the prognosis of the underlying heart disease present. In our series, the prognosis of the "intermittent" type was somewhat better than that of the "persistent" type.

The physiologic mechanism involved, the clinical symptomatology, the criteria for the clinical and electrocardiographic diagnosis, and the therapy of the attacks with particular reference to quinidine are discussed.

AUTHORS.

Peel, A. A. F.: Congenital Heart Block With Atrial and Ventricular Septal Defect. *Brit. Heart J.* 5: 11, 1943.

A case of atrial septal defect with ventricular septal defect and congenital complete heart block is described and discussed. The patient had fairly good health until she was 40 years of age, and was still working as a housekeeper at 46 years of age.

AUTHOR.

Campbell, M.: Congenital Complete Heart Block. *Brit. Heart J.* 5: 15, 1943.

The present condition of seven patients with congenital complete heart block, now aged 42, 36, 31, 28, 26, 25, and 22 years is reported. Full details about six of the cases were published nine years ago. All six and one other (first seen shortly after the paper was published) have been traced, a very satisfactory result after this interval of nine years, especially in war time.

All are alive and well, and their degree of activity could be taken as a fair cross section of the general public. Of the four men, two are working men, who, though rejected from the army, have led strenuous lives, both in their work and in their play, almost certainly doing more than they ought to as their hearts are not normal. One has been two years in the R.A.F. and has been passed for flying duties, and the fourth is a professional man who leads a normal life, with gardening and cycling in his spare time.

Of the three women the eldest does ordinary housework on a farm, but the other two lead rather more sheltered lives, possibly because their doctors discouraged them. One was at easy work till she developed tuberculosis a year before her marriage, and the other, after doing light duties at home for six years, has taken up sedentary work since the war. Except for the one case of tuberculosis, no unexpected developments have arisen in any case, and the one who had Stokes-Adams attacks in infancy has led the most strenuous life, with only two short periods of recurrences.

Congenital complete heart block is not rare. It is overlooked because the rate is relatively fast, about 40 to 56, and also because the possibility is not remembered.

If there are no special complications carrying special risks of their own, the prognosis is good, and it will probably prove that the condition is compatible with survival to old age.

AUTHOR.

Touroff, A. S. W.: Blood Cultures From Pulmonary Artery and Aorta in Patient With Infected Patent Ductus Arteriosus. *Proc. Soc. Exper. Biol. & Med.* 49: 568, 1942.

Blood was taken and cultured directly from the aorta and pulmonary artery during an operation for subacute bacterial endarteritis superimposed on patent ductus arteriosus. The results demonstrated that the lungs removed infective material from the circulating blood of human beings and that, in the type of case under consideration, infective material enters the peripheral circulation, at least in part, through the pulmonary circuit.

KERSHBAUM.

Roosen, R.: The Role of Human Microdiencephalus in the Pathogenesis of Degenerative Heart Disease. *Cardiologia* 6: 214, 1942.

The degenerative heart and vessel diseases are not primary, independent changes but conditions following human microdiencephalus.

AUTHOR.

Bramwell, C.: Signs Simulating Those of Mitral Stenosis. *Brit. Heart J.* 5: 24, 1943.

In a consecutive series of 835 recruits, a duplicated second heart sound (generally associated with an apical systolic murmur) was present in 157 cases.

The duplicated second heart sound was best heard when the patient lay on his left side; the reason for this is discussed. Duplication of the second heart sound

was much more common in men under 20 years of age than in older recruits. Seventy per cent of the men in whom it was present were considered fit for Grade 1. Radioscopy in these cases generally showed an increased prominence of the pulmonary arc.

Since the production of an obstructive murmur depends on the degree of obstruction relative to the velocity of the blood current, it is suggested that an increased rate of blood flow through a normal mitral orifice may be instrumental in producing: (a) the accentuation and roughening of the first heart sound heard in certain athletes, in thyrotoxicosis, and in other conditions in which the heart is over-acting, and (b) the duplicated second heart sound heard in healthy subjects. Both these signs are therefore regarded as signifying a "relative" mitral stenosis.

This hypothesis entails a physiologic conception of mitral stenosis based on the volume of blood which an orifice of a certain size can transmit in unit time.

AUTHOR.

Jager, B. V., and Ransmeier, J. C.: Constrictive Pericarditis Due to *Bacterium Tularensis*. Report of a Case and Review of Reported Cases of Pericarditis Occurring With Tularemia. Bull. Johns Hopkins Hosp. 72: 166, 1943.

The authors have presented a case of tularemia of the typhoidal type with evidence of pleuritis and pneumonia. The illness was complicated by a constricting pericarditis which persisted after clinical recovery from the febrile illness. Roentgenograms following instillation of air into the pericardial sac showed the pericardium to be markedly thickened. *B. tularensis* was recovered from the pleural fluid of this patient. In addition there was suggestive evidence that this organism was present in the pericardial fluid. The manifestations of nine additional cases of pericardial involvement in tularemia are tabulated and discussed.

AUTHORS.

Ditkowsky, S. P., Stevenson, E., and Campbell, J. M.: An Epidemic of Rheumatic Fever in a Children's Institution Following an Outbreak of Acute Tonsillitis. J. A. M. A. 121: 991, 1943.

An epidemic of rheumatic fever in a children's school followed an outbreak of acute tonsillitis. Two hundred forty-one children had acute hemolytic infections of the throat, and eighty-eight children in the institution showed manifestations of rheumatic fever. The conclusion reached after studying various features of the epidemic are:

The epidemiology of rheumatic fever is closely linked with that of streptococcal infections of the upper respiratory tract.

Familial predisposition on the basis of specific tissue susceptibility probably is an important factor in the pathogenesis of rheumatic fever.

The most susceptible age group appeared to be between 9 and 14 years. Sex did not appear to be a factor.

Sixty-two children (65 per cent) had histories compatible with previous rheumatic infections. Sixty-one children had systolic apical murmurs elicited before the present rheumatic attack, most of them having the characteristics ascribed to functional murmurs. This would suggest that the murmurs should be observed repeatedly before they are dismissed as insignificant.

No direct correlation could be made between meteorologic conditions and the incidence of rheumatic fever. It was felt that they were important so far as they were related to the seasonal incidence of infections of the upper respiratory tract.

AUTHORS.

Fox, T. T., and Kremer, H. S.: *The Heart in Pulmonary Tuberculosis: Studies of the Auricular Complex in the Electrocardiogram.* *Am. Rev. Tuberc.* 47: 135, 1943.

Electrocardiographic tracings of 804 patients with pulmonary tuberculosis were analyzed, with particular reference to the occurrence of abnormal auricular complexes.

Sixty-nine tracings were found to possess abnormal P waves; thirty-eight tracings in this group had notching and spiking in Leads II and III; sixteen out of the thirty-eight tracings were associated with clinical and roentgenological evidence of bilateral tuberculosis and emphysema.

Fifteen cases of severe emphysema were studied electrocardiographically. Eight cases had a low P₁, and a notched and spiked P₂ and P₃.

Fifteen cases with post-mortem evidence of right ventricular hypertrophy, without hypertrophy of the left ventricle, showed findings not fully confirmatory of the observations stated above. The predominant electrocardiographic abnormality in this group was an abnormal P₂.

To study the effect of change in position on the auricular complex, ten cases with changes in the P wave of Lead I had electrocardiograms taken in the supine, left lateral, and right lateral positions. Only six cases had directional changes in the QRS complex. All cases showed changes in the configuration of the P wave with change of position of the patient.

In order to see the effect of transient overfilling of the right auricle on the electrocardiogram, ten patients in congestive failure, with enlarged livers and prominent jugular veins, had tracings taken prior to, and after, pressure upon the liver sufficient to increase the volume of the jugular veins to a marked extent. No change took place in shape or amplitude of the previously normal P waves in the eight cases with sinus rhythm.

It is the authors' impression that P-wave changes cannot serve as a criterion for the existence of cor pulmonale in cases of pulmonary tuberculosis (or other gross pulmonary disease) where such information is most desirable. On the other hand, P-wave changes are frequently the sole electrocardiographic evidence of mediastinal displacement.

In the course of this study two additional interesting observations were made:

In a limited number of cases studied, inversion of the P₁ was almost universally associated with displacement due to right pneumothorax.

Changes in the measurable P-R interval in the electrocardiogram of cases with pulmonary tuberculosis may be due to mediastinal displacement or distortion. These changes are probably expressions of structural divergences of the P waves, and are not indicative of altered A-V conduction or shift in the pacemaker.

AUTHORS.

Fitz, R., Walker, B. S., and Branch, C. F.: *Polycythaemia Vera: Report of a Case.* *Arch. Int. Med.* 70: 919, 1942.

The case described appears unusual in that it is the first example of the disease to be described in which the clinical picture of polycythemia vera was seen to develop in a person previously regarded as normal, and in which its clinical earmarks disappeared under treatment, leaving behind a variety of interesting vestiges of its previous existence. The blood count had returned to normal in every way, and had remained normal for the rest of the patient's life. He died suddenly four and one-half years after his course of roentgen treatment had been completed. Examination of vertebral and sternal bone marrow, and of the spleen showed a degree of hematopoietic activity not ordinarily encountered in a person with chronic heart

failure. The individual died with a general vascular lesion which may have been related to the polycythemia. The authors discuss various phases of the situation and the possible causes of polycythemia.

McCulloch.

Grollman, A., and Rule, C.: Experimentally Induced Hypertension in Parabiotic Rats. *Am. J. Physiol.* 138: 587, 1943.

Rats were joined in parabiotic union and their systolic blood pressures determined daily, following operative procedures on the kidney. Parabiotic individuals retain an independence of their circulatory adjustments; hypertensive blood pressure levels may be maintained in one member of a parabiotic pair, while the blood pressure of the co-twin remains normal. In some instances, however, the hypertensive action induced by procedures on the kidney is transmitted to the intact co-twin. The results are interpreted as being most consistent with the view that the kidney normally elaborates a substance necessary for the maintenance of normal blood pressure levels. The bearing of the results on other current theories of the pathogenesis of experimental renal hypertension is discussed.

AUTHORS.

Abell, R. G., and Page, I. H.: The Effects of Renal Hypertension on the Vessels of the Ears of Rabbits. *J. Exper. Med.* 75: 673, 1942.

Experimental renal hypertension in rabbits causes persistent, visible constriction to occur in the arterioles of the ears which is not great enough to restrict the flow of blood to the tissues but is sufficient to increase peripheral resistance. The constriction is due to the direct action of a substance on the arterioles since it occurs in the absence of nerves to vessels. It is associated with the appearance of new arteriovenous anastomoses. Since many of these phenomena have been reproduced by injection of angiotonin, this evidence is consonant with the view that the hypertension is due to angiotonin or some similar substance.

AUTHORS.

Eichelberger, L.: The Distribution of Water and Electrolytes Between Blood and Skeletal Muscle in Experimental Hypertension. *J. Exper. Med.* 77: 205, 1943.

The effect of an abnormal renal circulation and a resulting hypertension on the distribution of water and electrolytes in skeletal muscle of dogs was as follows: By analysis of the muscle the total content of sodium and chloride was found increased, and the total potassium content decreased. A redistribution of water occurred in the muscle, involving a shift of water from the muscle cells to the extracellular phase (F) = 254, plus-minus 54 Gm., intracellular water (H_2O)_c = 532, plus-minus 47 Gm., and total solids (S) = 214, plus-minus 8 Gm. This extracellular phase volume of 254 Gm. represents an increase of 65 per cent over that found in normal dog muscle.

After subjecting the hypertensive dogs to large increases in total body water produced by the intravenous injection of normal isotonic salt solution, the total bulk of 1 kilogram of muscle increased a mean average of 103 Gm., of which one-half was attributed to the extracellular phase and one-half to the swelling of the muscle cells.

Whether the changes found in this study are the result of the functional disturbances caused by the experimental renal abnormalities, or the hypertension, or a combination of both is uncertain at this time. The significance of the results is that there is quantitative evidence that a redistribution of water has occurred in skeletal muscle so that a real extracellular edema exists.

AUTHOR.

Wiggers, C. J., Wégria, R., and Nickerson, N. D.: Reactions of the Aorta in Hemorrhagic Hypotension and Shock. *Am. J. Physiol.* 138: 491, 1943.

On the basis of negative evidence from three modes of experimental approach, the authors conclude that it appears highly improbable that active changes in the aortic wall play any role in the initiation or progression of hemorrhagic shock or in the establishment of an irreversible state.

AUTHORS.

Page, I. H., and Abell, R. G.: The State of the Vessels of the Mesentery in Shock Produced by Constricting the Limbs and the Behavior of the Vessels Following Hemorrhage. *J. Exper. Med.* 77: 215, 1943.

Direct observations of the arteries, arterioles, capillaries, veins, and lymphatics in the mesentery of anesthetized cats put into shock by incomplete occlusion of the circulation showed that:

Marked constriction of the arteries and arterioles, produced by muscular contraction, occurred usually within an hour after incomplete occlusion of the limbs, lasted several hours, and finally gave way in most instances to relaxation an hour or more before death. The constriction reduced the blood supply to the mesentery and intestine, and the venous return from them. It did not, however, interrupt the blood flow. No pooling or stagnation of blood was seen even as a terminal phenomenon.

The veins of the mesentery also became constricted, but showed less tendency to dilate as death approached. The lymphatics likewise became somewhat narrowed. Even during the terminal stage the leucocytes moved along without change in shape and without sticking to the walls of the capillaries or venules.

Hematocrit determinations showed progressive hemoconcentration of moderate degree.

Autopsy usually showed the presence of small hemorrhages in many parts of the body, especially the heart, liver, spleen, and lungs.

Bilateral nephrectomy, suprarenalectomy, and pancreatectomy did not significantly alter the morphologic picture elicited by shock induced by restriction of the circulation to the limbs.

Removal of large amounts of blood was always followed within a short time by constriction of arteries, arterioles, veins, and lymphatics of the mesentery.

Fall in arterial pressure produced by pitling was not accompanied by change in diameter of the arteries, arterioles, veins, or lymphatics, or by blanching of the mesentery or gut.

AUTHORS.

Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity. *Bull. Johns Hopkins Hosp.* 72: 65, 1943.

Typical diffuse periarteritis nodosa has been produced experimentally by establishing in rabbits a condition analogous to serum sickness in man.

These experiments demonstrate that periarteritis nodosa is one manifestation of the anaphylactic type of hypersensitivity.

The clinical and pathologic evidence, presented in previous papers, shows that periarteritis nodosa has developed in patients as a result of hypersensitive reactions following foreign serum and sulfonamide therapy. This is supported by the present experiments, and shows that widely different types of sensitizing antigens are capable of causing periarteritis nodosa in man, and suggests the advisability of attempting to discover and to eliminate the responsible antigen in each case diagnosed clinically.

The continued administration of foreign serum or sulfonamides after a hypersensitive reaction has occurred, or the injection of a single large amount of foreign

serum, increases the danger of producing the vascular damage by prolonging the contact of the sensitized body with the offending antigen.

Acute diffuse glomerulonephritis occurred in a number of the animals that developed a hypersensitive reaction to the foreign serum. This supports the view that some cases of glomerulonephritis in man may be due to hypersensitivity.

AUTHORS.

Steiner, A., and Domanski, B.: Serum Cholesterol Level in Coronary Arteriosclerosis. *Arch. Int. Med.* 71: 397, 1943.

The serum cholesterol level in patients with coronary arteriosclerosis is significantly higher than the serum cholesterol level in normal subjects.

The serum cholesterol level in patients with coronary arteriosclerosis is inconstant and fluctuates widely.

The claim of relative constancy of the serum cholesterol level in normal persons is further substantiated.

AUTHORS.

Loutit, J. F., Mollison, M. D., van der Walt, E. D.: Venous Pressure During Venesection and Blood Transfusion. *Brit. M. J.* 2: 658, 1942.

The venesection of normal subjects is accompanied by a fall in venous pressure. During the following thirty minutes there is a return toward the original venous pressure, although this level is not regained in this period.

During the transfusion of blood to unselected hospital patients there is, in the majority of cases, a rise of venous pressure which is approximately proportional to the amount given and occurs more frequently at the faster rates. Signs and symptoms suggestive of peripheral vasodilatation were encountered in three of the forty-three cases transfused. In these cases vasodilatation occurred after a rise in venous pressure and was not followed by a fall.

After transfusion, patients suffering from pulmonary disease showed signs of pulmonary congestion, as revealed by a reduction in vital capacity. This decrease was not related to the venous pressure changes.

AUTHORS.

Abramson, D. I., Flachs, K., Freiberg, J., and Mirsky, I. A.: Blood Flow in Extremities Affected by Anterior Poliomyelitis. *Arch. Int. Med.* 71: 391, 1943.

The rate of blood flow during rest was measured by the venous occlusion plethysmographic method in a series of twenty-seven subjects with acute or chronic anterior poliomyelitis of one extremity.

It was found that in the majority of cases the peripheral circulation in the paralyzed limb was the same as that in the contralateral normal extremity; in fact, in some instances it was significantly greater.

Evidence was obtained which indicated that the cutaneous blood vessels in the extremity affected by anterior poliomyelitis respond more markedly to the stimulus of cold than do those of the contralateral normal limb. The response takes the form of excessive vasoconstriction on exposure to a low environmental temperature, and is apparent as a significant decrease in cutaneous temperature.

By studying the changes in blood flow during the reactive hyperemia elicited by a period of arterial occlusion, some evidence was obtained which suggested that the metabolism of muscles atrophied by poliomyelitis is the same as that of normal tissues.

In view of the lack of evidence for the hypothesis that the peripheral circulation is reduced in persons with anterior poliomyelitis, it is concluded that those treatments which have for an aim the increase in blood flow through the affected parts should be critically re-examined for their therapeutic value.

AUTHORS.

Bordley, J., III, Gladston, M., and Dandy, W. E.: The Treatment of Essential Hypertension by Sympathectomy. A Report on Twelve Patients Three to Seven Years Following Operation. Bull. Johns Hopkins Hosp. 72: 127, 1943.

The presence of incapacitating symptoms was the only criterion for sympathectomy in twelve patients with essential hypertension.

The level of arterial pressure was lowered for six to eighteen months in four of the nine patients treated by the infradiaphragmatic operation (Adson-Craig), and for four and one-half years in one of the three patients treated by the supradiaphragmatic operation (Peet).

Symptomatic relief appeared to depend upon lowered arterial pressure in four of nine patients in whom it occurred.

In two patients abnormal findings in the heart and eye grounds regressed during the period of lowered arterial pressure and returned after the arterial pressure rose again.

Return of arterial pressure to preoperative hypertensive levels was not associated with regeneration of the sympathetic nerves supplying the lower extremities, which were severed during the Adson-Craig operation.

AUTHORS.

Chen, K. K., Hargreaves, C. C., and Robbins, E. B.: Comparison of Digoxin, Digilanids A, B, and C, and Deacetyldigilanids A and B. J. Am. Pharm. A. 31: 236, 1942.

Six glycosides of *Digitalis lanata*: digoxin, digilanids A, B, and C, and deacetyldigilanids A and B, have been assayed in cats and frogs. In cats, the order of activity from high to low is: digoxin and digilanid C, digilanids A and B, deacetyldigilanid A, deacetyldigilanid B. The results in frogs do not follow those in cats. The order of potency from high to low is: digilanid A, deacetyldigilanid A, digoxin, deacetyldigilanid B, digilanids B and C. The differences of the last three compounds are apparently not significant.

AUTHORS.

Chen, K. K., and Elderfield, R. C.: Synthetic Derivatives of Strophanthidin. J. Pharmacol. & Exper. Therap. 76: 81, 1942.

Strophanthidin acetate and seven synthetic glycosides of strophanthidin all have a digitalis-like action.

When assayed in cats and frogs, strophanthidin acetate, strophanthidin- β -D-glucoside, -D-xyloside, and -L-arabinoside, prove more potent than strophanthidin. Strophanthidin- β -tetraacetyl-D-glucoside, -triacyetyl-D-xyloside, -triacyetyl-L-arabinoside, and -tetraacetyl-D-galactoside, on the other hand, are weaker than strophanthidin.

Strophanthidin- β -D-glucoside and -L-arabinoside are also more potent than cymarín, the natural glycoside from which strophanthidin is originally obtained. Strophanthidin- β -D-xyloside is at least as active as cymarín.

AUTHORS.

Book Review

CLINICAL ROENTGENOLOGY OF THE CARDIOVASCULAR SYSTEM: By Hugo Roesler, M.D., F.A.C.P., Associate Professor of Roentgenology and Cardiologist, Department of Medicine, Temple University School of Medicine; Cardiologist, Temple University Hospital, Philadelphia. Second edition. Charles C Thomas, Springfield, Ill., 1943, 480 pages, 337 illustrations, \$7.50.

The second edition of this authoritative volume has made its position as the classic work in the field of cardiovascular roentgenology fully secure. Housed in a handsome binding, printed with great clarity, adorned with numerous and unusually well reproduced illustrations, the physical characteristics are in keeping with the nature of the contents, and both arouse enthusiasm on the part of the reviewer. Certainly no cardiologist, no internist, no roentgenologist can afford to be without this book.

The entire work has been revised; greater detail has been added to most of the chapters, and almost all the newest studies on roentgenologic examination of the heart have been included. The addition of about 135 pages of text, a similar number of new figures, and the inclusion of well over 2,500 references make the new edition most complete. The bibliography is particularly excellent; only a few of the important references of the past two years have been omitted. The increased material on roentgen technique is especially valuable. The author has also added a considerable amount of detail on contrast cardiography, on cardiac measurements, and on the secondary changes in the lungs incident to cardiac failure.

Obviously, there are some statements with which issue can be taken. For example, the conclusion that patency of the ductus arteriosus occurs more frequently in association with other congenital defects than as a solitary process is not in accord with the experience of investigators who have studied this problem in connection with the surgical treatment. It may apply to stillborns and young infants. The author's detailed description of the roentgenologic characteristics of patency of the ductus arteriosus, however, is most timely, and represents a conservative and well-grounded estimation of the value of x-ray examination. On the whole, there is very little with which to disagree and very much to commend. The work is thorough, painstaking, sound, and well presented. The second edition of this book is a tribute to the publishers, and particularly to the author, whose authority in this field is unquestionable.

LEO G. RIGLER.

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THE MECHANISM OF AURICULAR PAROXYSMAL TACHYCARDIA

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FRANKLIN D. JOHNSTON, M.D., ANN ARBOR, MICH.

AURICULAR paroxysmal tachycardia was long ago described and recognized as a clinical entity, but the fundamental mechanism or mechanisms responsible for this disorder have not yet been finally ascertained.^{1, 2} Unlike auricular flutter and auricular fibrillation, it cannot be readily induced in experimental animals, and cannot, therefore, be easily studied by this method. Speculations as to its nature must, therefore, be based on pertinent observations on man. We propose to discuss from this standpoint the following features of this disturbance: (1) the form of the auricular deflections; (2) the effects of exertion, vagal stimulation, digitalis, quinidine, and other drugs upon the auricular rate and the duration of the paroxysms; (3) similarities, differences, and relations between it and auricular flutter and fibrillation; (4) the spontaneous occurrence of auriculoventricular block in a small number of cases and the difficulty or impossibility of producing it in most of the others; and (5) the occurrence of alternation in the auricular cycle length. We wish particularly to examine the suggestion³ that auricular paroxysmal tachycardia is caused by circus rhythm involving one of the specialized auricular nodes.

When Mines⁴ described circus rhythm he suggested that it might be responsible for some cases of paroxysmal tachycardia in man. Hiesen and Sebastiani⁵ were among the first to suggest that auricular paroxysmal tachycardia is due to circus contraction. Their reasoning was based chiefly on the action of quinidine in this disorder. Lewis⁶ pointed out that the total amount of auricular muscle is not sufficiently large to accommodate a circus mechanism at known rates of conduction in auricular

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muscle and with cycles as long as those which occur in auricular paroxysmal tachycardia. For this reason and because of the isoelectric intervals separating the auricular deflections, he could not accept circus rhythm as the cause of this disorder. He did not mention the possibility that the path of the circus impulse might pass through one of the specialized auricular nodes. Ashman and Hull³ have suggested that in auricular paroxysmal tachycardia there is a circus rhythm in which the re-entrant impulse passes through one of the nodes. In a necessarily brief discussion they presented only a part of the evidence which supports this view. They mentioned especially the effects of vagal stimulation and the slowness of the rate, as compared with auricular flutter, in relation to the slowness of conduction through nodal tissue.

The Form of the Auricular Deflections.—The form of the auricular deflections was examined in the electrocardiograms of one hundred unselected cases of auricular paroxysmal tachycardia. In thirty-four they were upright in Leads I and II, and in many of these the P waves closely resembled, or were identical with, those recorded when normal sinus rhythm was present. In fourteen cases the auricular deflections were inverted in Leads II and III. In fifty cases these deflections were intermediate in form, very small, flat or diphasic, or they were not clearly visible because they were small and superimposed upon some part of the ventricular complex. In many of the cases in which there were upright P waves the impulse must have entered the main mass of auricular muscle near the normal pacemaker in the upper part of the sinoauricular node. The inverted P waves suggest beats arising in or near the auriculoventricular node, or in some outlying part of the auricular muscle. The point of origin of beats represented by auricular deflections of intermediate form cannot be stated with certainty. Lewis^{2, 6} has shown that deflections of this form may arise in a region between the upper part of the sinoauricular node and the auriculoventricular node, and that they may be produced by impulses arising in the lower part of the sinoauricular node. With two exceptions the form of the auricular deflections in the cases of auricular paroxysmal tachycardia which we reviewed is not inconsistent with the view that the paroxysmal focus lay in or near the sinoauricular node or in or near the auriculoventricular node. The exceptions were two cases in which the auricular deflections were inverted in Lead I and upright in Leads II and III. Such cases are very uncommon; in them the form of the auricular deflections suggests a focus located in the upper part of the left atrium.

The Stability of the Rate.—In auricular paroxysmal tachycardia the auricular rate is ordinarily remarkably constant. It is not, as a rule, influenced by rest, posture, emotion, or exertion. It is not under the control of the extrinsic cardiac nerves, as are slower rhythms of the normal type arising in the sinoauricular node or the auriculoventricular node. Even at the onset of attacks, and at the end of paroxysms terminating

spontaneously, there is usually little or no alteration of the rate. The patients with upright auricular deflections in Leads I and II, and especially those with atrioventricular block, show somewhat more variation in auricular rate than do those whose auricular waves are inverted or intermediate in form, with no block.

Exercise.—The auricular rate in auricular paroxysmal tachycardia is sometimes increased by exercise,^{7, 8} but in auricular fibrillation the opposite is usually observed.^{9†} Slowing of the fibrillating auricles on exertion is attributed to a reduction of vagal tone; atropine also slows the rate of the fibrillating auricles.¹¹ The acidosis accompanying exercise should, by depressing conduction in the auricles, tend further to reduce their rate.^{4, 12, 13} The occasional increase in the rate of auricular paroxysmal tachycardia on effort may be attributed to a reduction of vagal tone; acidosis should cause slowing, whatever the mechanism.

Stimulation of the Vagus.—In auricular paroxysmal tachycardia, pressure upon the carotid sinns and other measures which stimulate the vagus nerves not uncommonly slow the rate of the paroxysm and frequently restore normal rhythm.^{14, 15} As a rule the slowing occurs immediately preceding the termination of the attack, but occasionally the rate is slowed when the attack is not stopped.

Vagal stimulation diminishes the rate of impulse production in the sinoauricular and the auriculoventricular node, and depresses conduction in the latter. Its effect upon the rate of conduction in the sinoauricular node and upon the rate of impulse production in auricular muscle outside the nodes is not known. Vagal stimulation shortens the effective refractory period of ordinary auricular muscle and improves its conductivity. In disorders caused by circus rhythm in auricular muscle these effects tend to increase the number of cycles per minute.¹⁶ The slowing of the rate of paroxysmal tachycardia and the restoration of normal rhythm by vagal stimulation cannot be explained by the effect of increased vagal tone upon the characteristics of the ordinary auricular muscle, and are most logically attributed to the action of these nerves upon the nodes.

Digitalis.—Like vagal stimulation, digitalis often slows the rate of auricular paroxysmal tachycardia and restores normal rhythm.¹⁷ Occasionally the drug slows the rate without stopping the tachycardia, but usually the slowing occurs only a short time before the termination of the attack. Digitalis acts directly upon the heart muscle, and indirectly by stimulating the vagus nerves. In auricular fibrillation and flutter the increase in the circus rate produced by the drug is apparently caused primarily by increased vagal tone, which shortens the refractory period of the ordinary auricular muscle. The slowing of the ventricular rate

*Case 2.

†Dourner¹⁹ has observed in auricular flutter an increase in auricular rate after exercise. This is exceptional.

is due to both a direct and an indirect depression of the conductivity of the atrioventricular node. The effects of digitalis in paroxysmal auricular tachycardia cannot be attributed to shortening of the refractory period of the auricular muscle, and would seem to depend upon its nodal action or upon some effect as yet unknown. The effect of digitalis upon conduction within the sinoauricular node is not known. The direct action of the drug upon auricular muscle is to increase its effective refractory period and to depress its conductivity.^{18, 19} This effect can scarcely account for its ability to slow or abolish auricular paroxysmal tachycardia; it is opposed by the indirect vagal action of the drug upon the auricular muscle, and the effects of digitalization and vagal stimulation in the condition are similar, not opposite. The effect of the drug upon the rate of impulse production in auricular muscle outside the nodes is not known. If the slowing of the rate and the restoration of normal rhythm in auricular paroxysmal tachycardia are caused by any of the known effects of this drug, it would seem that they must be attributed to its effects upon nodal tissue.

Quinidine.—Quinidine and quinine likewise often slow the rate of auricular paroxysmal tachycardia and sometimes restore normal rhythm.^{5, 8, 20} These drugs, too, act upon the heart both directly and indirectly. The indirect effect is a reduction of vagal tone. In the auriculoventricular node the direct and vagal actions are opposed; the direct effect is to depress conduction and the indirect to improve it. Consequently, the changes in auriculoventricular conductivity are somewhat variable.²¹ In auricular muscle both the direct and the indirect actions increase the effective refractory period and depress conductivity. It is through these effects that these drugs invariably slow the circus rate and often restore normal rhythm in auricular fibrillation and flutter.^{19, 21, 22} In man they do not slow the rate of simple sinus tachycardia;^{20, 23} indeed, they often increase the rate of slower sinus rhythm.²⁰ In dogs both acceleration and slowing of the sinus rhythm have been observed under different conditions.^{21, 24, 25} It is difficult to understand how the known effects of these drugs upon conductivity and upon the effective refractory period can bring about slowing of the rate and restoration of normal rhythm in abnormal tachycardias not caused by circus rhythm.

Relation to Auricular Flutter and Fibrillation.—Auricular paroxysmal tachycardia sometimes changes spontaneously to auricular flutter or fibrillation, or flutter or fibrillation may change to paroxysmal tachycardia.^{26, 27, 28} In some cases digitalis may have converted paroxysmal tachycardia into fibrillation.^{7, 29} Such changes in rhythm, although not common, suggest a relationship between these disorders.

In the preceding paragraphs mention has been made of some of the similarities and differences between auricular paroxysmal tachycardia, on the one hand, and auricular flutter and fibrillation, on the other, with respect to the effects of exertion, vagal stimulation, digitalis, and

quinidine. Like paroxysmal flutter and fibrillation, auricular paroxysmal tachycardia begins and ends abruptly. The auricular rate in paroxysmal tachycardia, as in flutter and fibrillation, is quite stable; it is not often influenced appreciably by rest, posture, emotion, or exercise, as is the normal sinus rhythm. Auricular paroxysmal tachycardia with partial auriculoventricular block resembles auricular flutter in many respects.^{5, 30} Quinidine usually slows the heart rate in paroxysmal tachycardia, and always slows the circus rate in fibrillation and flutter, but does not slow sinus tachycardia. These features of auricular paroxysmal tachycardia suggest that its mechanism, like that of flutter and fibrillation, may depend on circus rhythm.

The mechanism of auricular paroxysmal tachycardia cannot, however, be a circus contraction involving ordinary auricular muscle only, like that of auricular flutter or fibrillation. In some instances exercise increases the rate of auricular paroxysmal tachycardia, but it usually slows the rate of the fibrillating auricles. Vagal stimulation and digitalis often slow the rate of paroxysmal tachycardia, whereas, in flutter and fibrillation, they increase the circus rate. Furthermore, as pointed out by Lewis,² the total amount of auricular muscle is not sufficiently large to accommodate a circus mechanism at known rates of conduction and with cycles as long as those of auricular paroxysmal tachycardia. In addition, the auricular deflections of paroxysmal tachycardia, unlike those of flutter, are separated by intervals of electrical quiescence, in which the galvanometer string is at rest in the isoelectric position.^{2, 7, 31}

The separation of the auricular deflections of paroxysmal tachycardia by isoelectric intervals is shown commonly in standard leads, usually in chest leads, and always in esophageal leads; it is most clearly seen in cases of tachycardia with auriculoventricular block in those auricular cycles which are entirely free of ventricular deflections.^{7, 31} This is quite different from flutter, in which the electrocardiographic oscillations are continuous; the tracing never comes completely to rest at the isoelectric line. Complete separation of the auricular deflections is inconsistent with circus rhythm unless some way is found to account adequately for isoelectric intervals during the continuous activity of the circus movement. They could be accounted for if the circus path traversed either the sinoauricular or the auriculoventricular node. While the advancing wave of activity was passing through the node, the amount of tissue entering the active state would be too small to produce electrical forces detectable by present methods. The observed auricular deflection would be inscribed by the activation of auricular muscle after the impulse emerged from the node. Its form and direction would be governed by the point at which the impulse entered the main body of the auricular muscle. Impulses emerging from the upper part of the sinoauricular node should give rise to upright deflections not unlike those of normal rhythm, impulses emerging from the atrioventricular

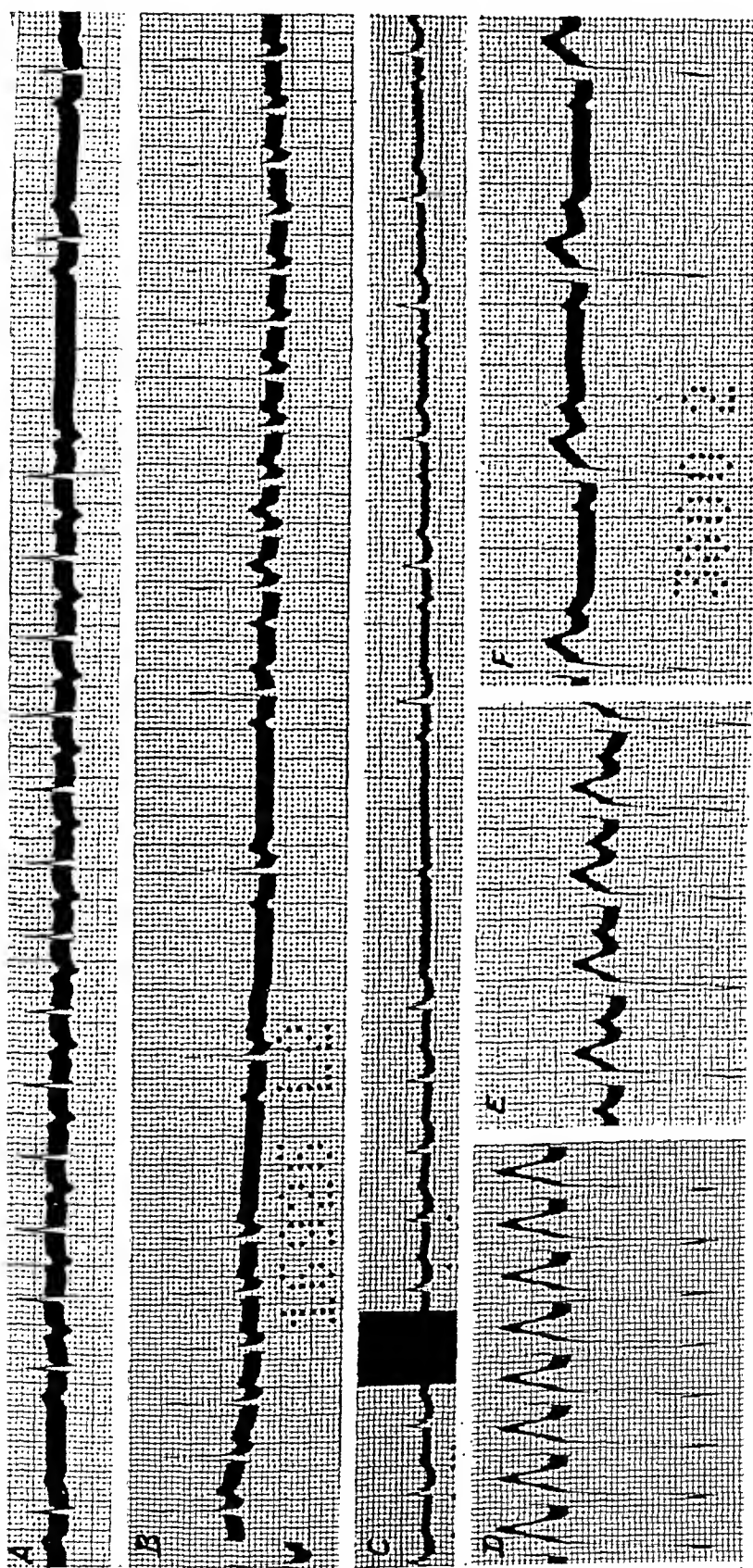


Fig. 1.—Electrocardiograms illustrating the relationship between the termination of attacks of auricular paroxysmal tachycardia and depression of atrioventricular conductivity. A, Lead II: a paroxysm ends spontaneously with an abnormal auricular beat which is blocked. B, Lead II: deep breathing; the P-R interval is prolonged (0.28 second) after the first normal auricular beat, and somewhat shorter (0.24 to 0.22 second) in subsequent beats. C, Lead II: pressure upon the carotid sinus; the first normal auricular beat is blocked. D, E, and F, chest leads: the paroxysm (D) was stopped by digitalis; normal rhythm (E) was followed almost immediately by 2 to 1 atrioventricular block (F).

node should give rise to inverted deflections like those of atrioventricular rhythm, and deflections of intermediate form might be produced by impulses emerging from the lower part of the sinoauricular node.^{5, 6} In a mechanism such as this a circus rhythm could be accommodated in auricular muscle and in one of the specialized nodes at known rates of conduction and with cycle lengths such as occur in auricular paroxysmal tachycardia. The rate of the tachycardia would depend chiefly upon the speed of conduction and the length of the path within the nodal tissue.

Auriculoventricular Block.—Auriculoventricular block is extremely rare in those cases in which inversion of the auricular deflections suggests that the paroxysmal focus lies in or near the auriculoventricular node. It seems strange, in view of the high auricular rate, that block should occur so rarely. The most reasonable explanation would seem to be that the agents which tend to produce block, namely, vagal stimulation and digitalis, terminate the paroxysm before block occurs. It is easy to understand that this might happen in tachycardia which is dependent upon circus rhythm involving the atrioventricular node. At any rate, it appears that, in many cases of this kind, unimpaired conduction in this node is essential to maintenance of the paroxysmal tachycardia, and that depression of conduction in this node is intimately related to the termination of the attacks.

Not infrequently this relationship is apparent when the end of the paroxysm is recorded; sometimes the last paroxysmal auricular impulse is blocked, or block appears immediately after the cessation of the attack. Several electrocardiograms illustrating this phenomenon are shown in Fig. 1. Curve A (Lead II) shows a short attack of auricular paroxysmal tachycardia in its entirety. It begins with a premature inverted auricular deflection which resembles an auricular extrasystole, and ends spontaneously with a similar beat which is blocked. The P-R interval is slightly prolonged (0.24 second), both during the normal and during the abnormal rhythm. The last four cycles of the paroxysm are longer than those that precede them. A somewhat more complicated disturbance is shown in Curve B; in this case, deep breathing temporarily stopped an attack of auricular paroxysmal tachycardia. During the paroxysm the P-R interval was prolonged and the inverted auricular deflections (Lead II) followed closely the R waves of the preceding beats. The attack ended with a blocked auricular beat. The first and second beats after the end of the paroxysm are complicated by blocked auricular extrasystoles, as shown by the inverted auricular deflections which closely follow the R waves. The third beat is not so disturbed, but the fourth beat is followed immediately by a similar premature auricular beat which initiates another paroxysm of tachycardia. The P-R interval is abnormally long (0.28 second) after the first normal auricular beat, and somewhat shorter (0.24 to 0.22 second) in subsequent beats—the patient had received digitalis. In a third patient (Tracing

C) pressure upon the carotid sinus stopped the paroxysm. The auricular deflections (Lead II) are not clearly visible during the tachycardia. The first normal auricular beat is blocked, and subsequently the P-R interval is prolonged (0.25 to 0.27 second). In a fourth case the paroxysm (Curve D) was stopped by a large dose of digitalis given intravenously; the onset of normal rhythm (Curve E) was followed almost immediately by 2 to 1 atrioventricular block (Curve F). These last curves were obtained by means of a chest lead.

Partial auriculoventricular block occurs spontaneously in a few patients with auricular paroxysmal tachycardia, and it can be induced by vagal stimulation, or by digitalis, in a few others. In the great majority of all the cases in which block is present or can be induced, the P waves are similar in form to those recorded when normal sinus rhythm is present.⁷ It is conceivable that in such cases the tachycardia is caused by circus rhythm involving the sinoauricular node, and that agents which tend to induce atrioventricular block do not depress conductivity within the sinoauricular node sufficiently to block the circus path. The auricular rate appears to be notably more variable in this group of cases than in those in which block cannot be induced.

It should be pointed out, however, that block cannot be induced in many cases in which the form of the P wave suggests that the paroxysmal focus lies in or near the sinoauricular node, and also that it occasionally occurs or can be induced in cases in which the form of the P waves suggests that the paroxysmal focus lies in or near the atrioventricular node.

Alternation of Cycle Length.—In a small proportion of cases of auricular paroxysmal tachycardia there occurs a slight irregularity characterized by alternation of relatively long and relatively short auricular cycles.³² This has been observed in auricular flutter, also.³³ This phenomenon can be explained most satisfactorily by assuming that the mechanism of auricular paroxysmal tachycardia is circus rhythm.³²

DISCUSSION

The various features of auricular paroxysmal tachycardia which have been discussed suggest that (1) the specialized nodes are involved in its mechanism, (2) the abnormal mechanism is circus rhythm, and (3) the circus rhythm is of a special kind. That the specialized nodes participate in the abnormal mechanism is suggested by (1) the form of the auricular deflections, (2) the acceleration of the auricular rate by exercise, (3) the slowing of the auricular rate and the termination of attacks by vagal stimulation and by digitalis, and (4) the rarity of atrioventricular block, especially in paroxysms arising in the region of the auriculoventricular node. That the mechanism of the disorder is circus rhythm is suggested by (1) the abrupt onset and termination of attacks, (2) the remarkable stability of the rate, (3) the slowing of the auricular rate and the termination of paroxysms by quinidine, and (4) the occasional alternation of

cycle length. That the circus rhythm is of a special kind is indicated by (1) the slowing of the auricular rate and the termination of attacks by vagal stimulation and by digitalis, (2) the acceleration of the auricular rate by exercise, (3) the relatively slow rate and long cycle length, and (4) the separation of the auricular deflections by isoelectric intervals.

A circus rhythm involving in its path one of the specialized auricular nodes most adequately accounts for these features of auricular paroxysmal tachycardia. No one of them is of itself decisive, but all together point strongly toward this mechanism. It accounts most satisfactorily for the abrupt onset and termination of the paroxysms, the stability of the rate, the form of the auricular deflections and their separation by isoelectric intervals, the relatively slow rate and long cycle length, the rarity of atrioventricular block and the impossibility of producing it in most cases, the acceleration of the rate by exercise, and the slowing of the rate and termination of attacks by vagal stimulation, digitalis, and quinidine.

It is necessary, however, to consider several exceptions which cannot readily be explained in this manner. One exception is represented by the rare cases which resemble paroxysmal tachycardia but in which the rate slows gradually to normal.^{34, 35} In these cases the auricular deflections are identical with those which occur during normal sinus rhythm. They are probably not examples of true auricular paroxysmal tachycardia of the type under discussion, but rather of an unusual and persistent type of sinus tachycardia. Another apparent inconsistency is represented by those rare cases of auricular paroxysmal tachycardia in which there are auricular deflections of varying form.^{7, 8, 27, 36, 37} They suggest that the impulses originate in two different regions of the auricles. The explanation for this is not apparent. If the mechanism in these cases is circus rhythm, the circus path in the auricles must change markedly, or there must be two different regions of circus activity. A third exception is represented by the cases in which the auricular deflections are inverted in Lead I and upward in Leads II and III. The form of the deflections suggests that they arise in the upper part of the left atrium, far from the nodes of specialized tissue. Such cases are decidedly uncommon; there were only two among our one hundred unselected cases. All of these exceptions are rare, and need not influence our main conclusions.

In the light of the available evidence, which, if not conclusive, is at least very strong, we suggest that the view that auricular paroxysmal tachycardia is caused by circus rhythm involving one of the specialized nodes—the sinoauricular or the auriculoventricular node—deserves serious consideration.

*Case 15.

SUMMARY AND CONCLUSIONS

1. Many of the important features of auricular paroxysmal tachycardia have been considered from the standpoint of their significance in elucidating the mechanism underlying this disorder.

2. The slowing of the auricular rate and the termination of the paroxysms by vagal stimulation and by digitalis and the acceleration of the rate by exercise suggest that the abnormal mechanism is influenced by the action of these agents upon one of the specialized auricular nodes.

3. The form of the auricular deflections indicates that they originate in or near these nodes.

4. The extreme rarity of atrioventricular block in cases in which there are inverted auricular deflections suggests that in these cases the auriculoventricular node is involved in the abnormal mechanism.

5. The abrupt onset and termination of the attacks, the remarkable stability of the rate, the slowing of the auricular rate and the termination of the attacks by quinidine, and the occasional alternation in cycle length suggest that the abnormal mechanism is circus rhythm.

6. The slowing of the auricular rate and the termination of the attacks by vagal stimulation and by digitalis, the acceleration of the rate by exercise, the relatively slow rate and long cycle length, and the separation of the auricular deflections by isoelectric intervals suggest that the circus rhythm is of a special kind.

7. No one of the above features is of itself decisive, but all together point strongly toward circus rhythm in the auricles, the path of which passes through one of the specialized auricular nodes, as the underlying mechanism of auricular paroxysmal tachycardia. This mechanism accounts most satisfactorily for all of the above features.

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PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA WITH A-V BLOCK

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THEORETICALLY, extremely rapid heart action would be expected to produce fatigue and block in the conduction pathways rather frequently. Atrioventricular block in the presence of paroxysmal tachycardia is generally considered uncommon. Our experiences have led us to believe, however, that the occurrence is much more frequent than heretofore suspected.

A survey of the literature on cases of paroxysmal supraventricular tachycardia in which the diagnosis was confirmed by electrocardiographic studies would lead to the conclusion that atrioventricular block is only occasionally recorded during paroxysms of atrial tachycardia. There is a paucity of reports of such cases; after Lewis'¹ original observation, in 1909, it was fifteen years before the next case was put on record by Drury,² in 1924. The paper by Sprague and White,³ in 1925, seems to be the only study directed toward determining the frequency of this condition. Campbell and Elliott^{3a} did not mention finding block in forty-two electrocardiograms taken in a series of one hundred patients with paroxysmal supraventricular tachycardia. A few isolated cases of paroxysmal atrial tachycardia with block have been reported, but no large series has been studied.

Paroxysmal tachycardia does occur frequently in the youthful undamaged heart and is quite generally considered innocuous, but we cannot accept its presence as a guarantee that the heart is normal. We have furthermore found that block occurs much more frequently in patients with serious heart disease. The defective conduction complications may be of serious prognostic significance. The possible precipitating factors of serious paroxysmal tachycardias with A-V block have interested us.

HISTORICAL REVIEW

Sir Thomas Lewis¹ recorded with a polygraph, as early as 1909, A-V block in the presence of paroxysmal atrial tachycardia. At that time he described extensive observations in two cases, in the second of which there were frequent dropped ventricular beats which, at times, led to halving of the ventricular rate. The polygram (Fig. 14, p. 64) shows the conduction defect.

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Drury,² in 1924, reported an instance of paroxysmal tachycardia of nodal origin with variable retrograde A-V block. The published tracing shows gradual prolongation of the R-P interval, with eventual disappearance of the P wave, a "retrograde Wenckebach" phenomenon. In some portions of the tracing, where there is a long R-P interval, a reciprocal ventricular beat is recorded.

Sprague and White,³ in 1925, found three cases of A-V block among fifty-six cases of paroxysmal tachycardia in which records had been taken at the Massachusetts General Hospital during the preceding decade; a total of 5,085 patients had electrocardiograms taken. The first case was that of a 48-year-old woman who had bilateral cervical ribs and was thought to have rheumatic mitral disease. The tracings indicated the presence of two ectopic auricular foci, one or the other being responsible for the numerous paroxysms. Although the ventricle was able to preserve 1:1 conduction with an auricular rate as high as 270 per minute, albeit with intermittent QRS aberration, on other occasions there was varying A-V block, 3:2, 2:1, 3:1, etc., at atrial rates as low as 200 per minute, with no definite relation between the rate and block. Digitalization was of benefit, and removal of the cervical ribs appeared to give partial relief. The patient was sensitive to quinidine.

The second case was that of a 23-year-old woman without definite heart disease. At an atrial rate of 220, the ventricular rate was 110; after exercise the grade of block decreased to 4:3 or 3:2, and was of the Wenckebach type. Digitalis was thought to be beneficial in decreasing the number of attacks. The third case recorded by Sprague and White was that of a 26-year-old man without physical abnormality. The electrocardiograms showed frequent atrial premature beats. Other tracings during paroxysms showed occasional prolongation of the P-R interval, but with conduction to the ventricle. On other occasions there was gradual prolongation of the P-R interval, with block varying from approximately 10:9 to 2:1.

Since Sprague and White's paper, isolated cases have been reported. William Dock⁴ described an instance of paroxysmal atrial tachycardia with an atrial rate of 180 to 186, in which block varying from 2:1 to 4:1 was noted. He specifically differentiated this from atrial flutter because of the absence of evidence in any lead of continuous atrial electrical activity. Vagus and ocular pressure failed to affect the atrial rate, and did not raise the grade of A-V block above 4:1. Heyl⁵ studied a white man, 50 years old, with early congestive heart failure, whose paroxysms appeared after digitalization. That the drug precipitated the paroxysms was clearly proved by alternating periods with and without digitalis; 2:1 block was found frequently. On one occasion, change from the supine to the sitting position was shown to convert 2:1 A-V conduction to 1:1. These changes also occurred spontaneously. Reflex vagal stimulation, ineffective without digitalization, after varying doses of digitalis

produced conduction effects ranging from 2:1, 3:1, and 5:1 block to complete ventricular standstill.

Lanbry and Deglaude⁶ reported an instance of supraventricular tachycardia with a rate of 200 per minute in which there was slight cyclic variation of the P-R intervals, and also alternation of the R waves. Brown⁷ showed several instances of A-V block in paroxysmal tachycardia in his study of atrial mechanism disorders by means of an esophageal electrode. Gerandel⁸ followed an interesting case from 1926 to 1931. When first seen, the patient, 63 years of age, with hypertension, had evidence of cardiac failure while the ventricular rate was 172 per minute. Sudden cessation of the symptoms was associated with a fall in the ventricular rate to 86, which was shown electrocardiographically to be due to 2:1 A-V block. Change in position might initiate a change in conduction; thus, lowering of the head, standing up, or change from side to side in bed would abolish the block. Later tracings showed Wenckebach periods, with 5:4 or 4:3 conduction. In 1928 auricular fibrillation developed and persisted until 1931, when he was last seen.

Maddox⁹ studied carefully a patient with a persistently rapid atrial rate. While the rate was 160 per minute, carotid sinus pressure caused a 3:2 block of the Wenckebach type. Digoxin (0.5 mg.) was given intravenously, and slowed the atrial rate to 120, but with progressive prolongation of the P-R interval and dropped beats. On another day, when the patient was lying down, there was a ventricular rate of 56, with a 3:1 block. Exercise then caused a sudden rise of the pulse rate to 168; at this time, carotid sinus pressure led to an irregular pulse, with coupling. During sleep the ventricular rate fell to 80-90 as a result of A-V block, but, when the patient was awake, the heart rate rose to approximately 160. After thirty-six days in bed, the atrial rate had fallen to 70, but the abnormalities of the P wave persisted. Quinine, quinidine, acetylcholine, adrenalin, and atropine were used, but failed to abolish the abnormal mechanism. Three months later, the patient was seen again with a ventricular rate of 168 per minute, which slowed with pressure on the right carotid sinus. Pressure on the left side was without effect.

Fine and Miller¹⁰ have recently reported their observations on a patient who precipitated paroxysms of tachycardia whenever he sat up or stood up, unless this tendency was controlled by quinidine or digitalis. The rate varied from 120 to 200 per minute, depending on the posture. One tracing showed Wenckebach periods, and another, electrical alternation of the QRS complexes. The authors attributed the postural influence to vagal inhibition, mediated either through reflexes from the lower extremities or the carotid sinus, or because of changes in the cerebral blood flow. In support of this concept that vagus inhibition may coincide with the onset of paroxysmal tachycardia, instances were cited

in which paroxysms were precipitated by atropine, by adrenalin, or by actual vagus nerve disease and degeneration.

In a study of the influence of carotid sinus hypersensitivity in cardiac arrhythmias, Tanney and Lilienfeld¹¹ described the case of a 9-year-old girl who had had chorea three months previously, without demonstrable cardiac damage. When seen by them she had acute rheumatic fever, with mitral and aortic valvulitis. During an attack of paroxysmal tachycardia in which the rate was 150 per minute, carotid sinus pressure was applied. This produced complete A-V block, with ventricular asystole for 8.4 seconds, while the atrial rate slowed to 60 to 84 per minute. Partial A-V conduction then was resumed with an atrial rate of 94, and increasing, but with 2:1 block for 5.4 seconds. This was followed by 1:1 conduction, but with prolongation of the A-V conduction time.

Two of the current texts on electrocardiography illustrate A-V block in supraventricular paroxysmal tachycardia. Scherf and Boyd¹² show 2:1 block and Wenckebach periods. Katz¹³ illustrates delayed A-V conduction, with Wenckebach phenomena and electrical alternation, 2:1 block, and alternation of P-R conduction time and P-P cycle length. Few clinical data accompany these records.

Medical literature contains a few tracings which appear to justify a diagnosis of paroxysmal atrial tachycardia with A-V block, but which have been otherwise interpreted. For example, Marvin,¹⁴ in his discussion of ventricular tachycardia with alternating complexes, includes a case (No. 3) which appears capable of being interpreted as follows: Fig. 9 shows an atrial rate of about 200, and the first part of the tracings shows Wenckebach periods, with 3:2 and 2:1 A-V block. When 1:1 conduction is present, there is QRS aberration, usually with alternation and delay in intraventricular conduction. Likewise, Katz' book contains figures whose interpretation might be open to question (Fig. 308c, 317d). Doumer¹⁵ reported a case as nodal tachycardia which appears actually to be auricular flutter. The case reported by Savy, et al.,¹⁶ shows variable prolongation in A-V conduction, with interference dissociation.*

THE CRITERIA FOR THE DIAGNOSIS OF PAROXYSMAL ATRIAL TACHYCARDIA

These difficulties in interpretation raise the question of the criteria which must be applied to substantiate the diagnosis of *auricular or atrial tachycardia*, and particularly its differentiation from flutter. The classical criteria set down by Lewis¹⁷ need some modification. His definitions may be summarized as follows:

*In the few months since submitting this manuscript for publication, an excellent paper on this topic has appeared (Clarke, P. S., Wilson, F. N., Johnston, E. D., and Wishart, S. W.: Auricular Paroxysmal Tachycardia With Auriculoventricular Block, *AM. HEART J.* 25: 765, 1943). During this time, also, nine additional cases of paroxysmal tachycardia with A-V block have occurred, bringing the total in our files to forty-nine cases.

Paroxysmal tachycardia is characterized by the following: (1) onset and ending are abrupt; (2) first atrial response is premature; (3) it ends with a pause; (4) atrial rhythm is remarkably regular, with a maximal difference of less than 0.01 second; (5) with rare exceptions, exercise, posture, atropine, and vagus stimulation do not affect the atrial rate; (6) duration of more than ten days is rare; (7) an anomalous P wave, indicating an ectopic focus, may be shown, although sometimes the difference from the P wave of sinus origin is very slight (this is particularly so in the cases showing A-V block); (8) QRS aberration is frequent.

Auricular flutter is characterized as follows: (1) It is usually an established condition, although occasionally it is transient and repeated; (2) the atrial rate varies from 220 to 370, averaging 300 per minute; (3) the atrial rate is constant; (4) the atrial rate is unaffected by exercise, posture, atropine, and vagal stimulation; (5) in Lead I the atrial complexes are diminutive; in Leads II and III they show a sharp ascent, a blunt summit, and a gradual return; (6) "the complexes are contiguous; the string is moving constantly and rests for no measurable period on a base line."

MODERN CRITERIA IN SUMMARY

There is sometimes great difficulty in differentiating paroxysmal atrial tachycardia, flutter, and sinus tachycardia. Although there are rules for general application, nearly all are subject to exceptions, as is well recognized, and we have no absolute criteria for the diagnosis of ectopic atrial tachycardia. A sudden onset and termination are more likely in paroxysmal tachycardia than in flutter; a long duration is more likely in flutter. Carotid sinus pressure is much more likely to affect A-V conduction in flutter than in tachycardia; high atrial rates (above 280) are almost invariably the result of flutter. Moderately high atrial and ventricular rates (about 200, rarely above 240 or 260, and only occasionally below 160) are found in paroxysmal atrial tachycardia. All of these are helpful, but not absolute, rules. When the atrial rate is below 180 or 160, clear demonstration of an aberrant, ectopic P wave distinguishes paroxysmal from sinus tachycardia. A definite isoelectric segment indicating suspension of auricular activity, and hence the absence of a circus mechanism, distinguishes tachycardia from flutter. No other absolute criteria are available. Employing these, however, we have found a goodly number of instances of A-V conduction disturbance during paroxysms of atrial tachycardia. We have had a few cases in which all three cardiac mechanism disorders, namely, atrial tachycardia, flutter, and fibrillation, have been recorded, so that we cannot argue that the presence of flutter at one time rules out the possibility of paroxysmal tachycardia at another time. Paroxysmal tachycardia may be the result of a different type of circus rhythm.

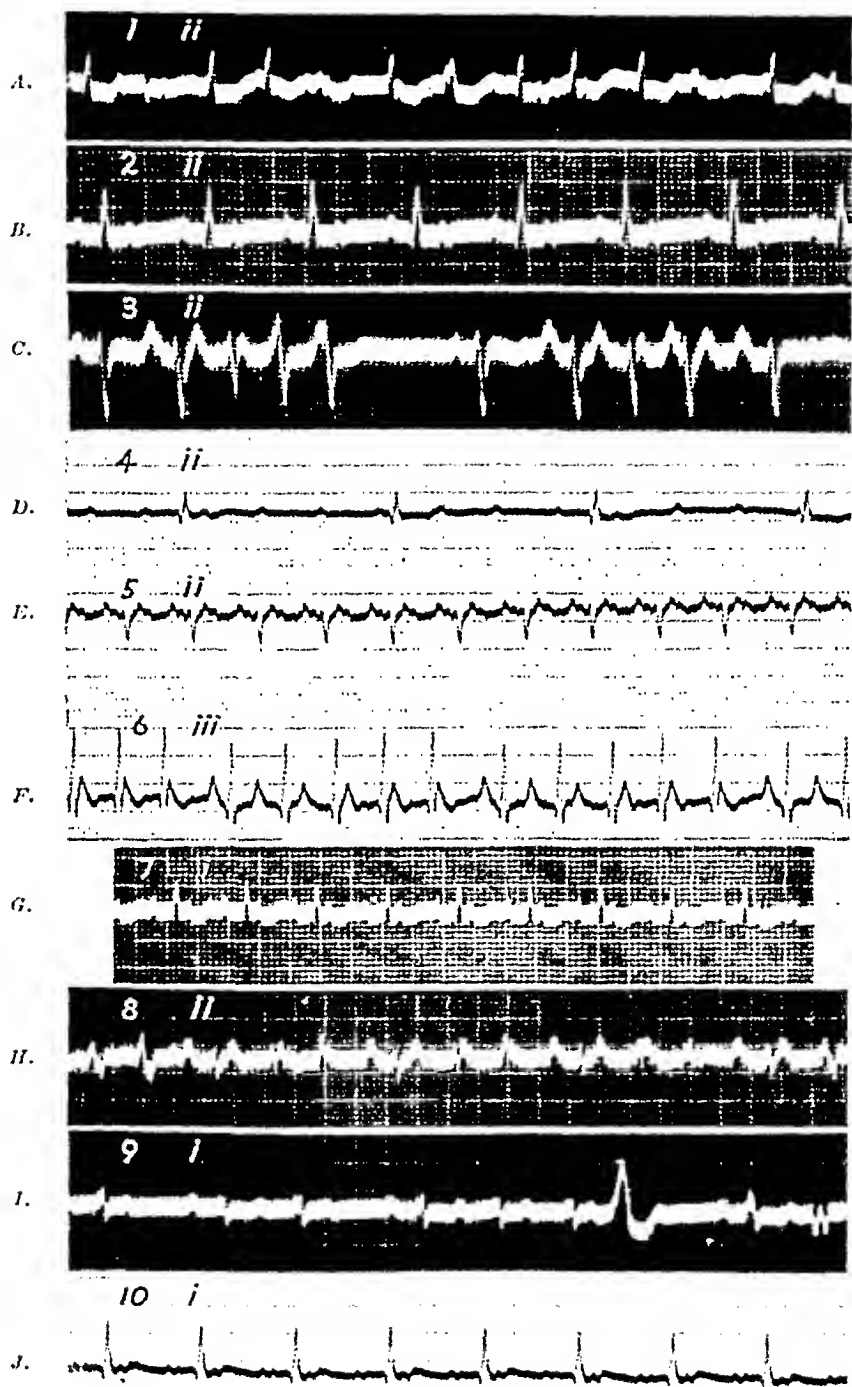


Fig. 1.

ABSTRACTS OF CASE RECORDS

CASE 1.—M. G., a colored man, aged 46 years, John Sealy Hospital No. 29976, was admitted Jan. 17, 1931, with congestive heart failure and general anasarca. The previous year he had hyperthyroidism and atrial fibrillation, and a thyroidec-tomy was done. The myocardial damage had persisted. During his first four days in the hospital he received 24 grains of digitalis, which caused a brisk diuresis and a rapid loss of 21 pounds in weight.

On the fifth hospital day his heart rate was 176 per minute, the rhythm was regular, and electrocardiograms showed that he had atrial paroxysmal tachycardia. Six cubic centimeters of digifolin were given intramuscularly, and twenty minutes later the rate had increased to 190 per minute and the electrocardiogram (Fig. 1, A, Lead II) showed a variable grade of A-V block of the Wenckebach type, usually 4:3 and 3:2. Note the slight differences in the cycle length.

The patient died on his sixth hospital day. At necropsy his heart was found to be enlarged, weighing 530 grams. There were myocardial scarring and fibrinous pericarditis. The lungs showed infarcts as well as some pneumonitis. The kidneys showed arteriolar disease. There were bilateral hydrothorax and chronic passive congestion.

CASE 2.—A. R., a colored man, aged 47 years, John Sealy Hospital No. 17146, was admitted Nov. 19, 1933, with congestive heart failure of about two months' duration. The failure had been precipitated by a respiratory infection. On November 25 hemoptysis was noted, and on that day 12 c.c., equivalent to 6 cat units, of digalen were given in the morning and 2 cat units in the afternoon. The following day, November 26, 4 more cat units were given, and electrocardiograms taken the same day (Fig. 1, B, Lead II) showed that he had atrial tachycardia with an atrial rate of 184 and a ventricular rate of 92, indicating 2:1 A-V block. Two days later there was sinus rhythm with a rate of 90 per minute. The patient's blood pressure was 98/74. The clinical diagnosis was arteriosclerotic heart disease, with cardiac enlargement and congestive heart failure. He improved under further treatment and was discharged from the hospital Dec. 24, 1933.

CASE 3.—W. H., a white man, aged 65 years, Electrocardiogram No. 1179, was seen as an outpatient on May 17, 1933, because of dull, aching pain in the pre-cordial area and upper abdomen. His blood pressure was 180/80 and he showed signs of generalized arteriosclerosis. Previous electrocardiograms had shown numerous atrial premature beats. On May 17 electrocardiograms (Fig. 1, C, Lead II) showed short paroxysms of atrial tachycardia at a rate of 272 per minute, with a varying Wenckebach type of A-V block. No medication was given at this time, although guanidine was used later for control of these paroxysms.

CASE 4.—J. K., a colored man, aged 56 years, John Sealy Hospital No. 45983, was admitted Oct. 4, 1934, with congestive heart failure which had been present for four months. His blood pressure was 168/130; there was marked peripheral arterio-sclerosis; gallop rhythm was present; and there was fluid in the right pleural sac, with extensive dependent edema. On October 3 electrocardiograms showed an atrial rate of 187, with 2:1 heart block. On October 4 the atrial rate was 194; on October 5 there was sinus rhythm with a rate of 90 per minute. On October 6 the atrial rate was 158, and carotid sinus pressure increased the grade of A-V block to 4:1 and higher (Fig. 1, D, Lead II). On October 8 the atrial rate had gone up again to 190 per minute. Later tracings showed sinus rhythm.

The patient had a stormy course in the hospital, with multiple emboli, including one in the left leg necessitating amputation, and another in the lower lobe of the right lung. The last embolus produced right-sided hemiplegia, shortly after which he died. Necropsy showed that the heart was enlarged, weighing 640 grams. There

was marked arteriosclerosis of the coronary vessels, with an old myocardial infarct and mural thrombosis at this point. Pulmonary infarction was present, and there were thrombi in the aorta and iliac arteries.

CASE 5.—L. B., a colored man, aged 83 years, John Sealy Hospital No. 46741, was admitted Feb. 12, 1935, with moderate congestive heart failure. He had had the anginal syndrome and congestive failure for two years. The blood pressure was 130/100. The heart was enlarged to the left and the aortic second sound was markedly accentuated. Previous electrocardiograms had shown marked left axis deviation and numerous ventricular and atrial premature contractions. On March 2 the electrocardiogram (Fig. 1, E, Lead II) showed an atrial rate of 250 per minute, with 2:1 A-V block. On March 8 the atrial rate was 255 per minute, and there was still a 2:1 A-V block; on this day 8 cat units of digitalin were given in four doses, and this changed the mechanism to sinus rhythm at a rate of 100 per minute.

After this he improved markedly, and was discharged April 19. However, he returned to the hospital with congestive failure on May 23, and again on Sept. 6, 1935, at which time he died. At necropsy the heart weighed 560 grams and showed marked coronary arteriosclerosis and a thrombus in the right auricular appendage. The kidneys showed arteriolar disease.

CASE 6.—J. V., a white woman, aged 27 years, Electrocardiogram No. 787, had been under observation as an outpatient for fourteen years because of frequent paroxysms of tachycardia. She had no demonstrable heart disease. There were numerous electrocardiographic records of paroxysms on file, with an atrial rate of 146 to 174 per minute. In an attempt to control her paroxysms she had been started on moderate doses of digitalis on Nov. 1, 1934, and had been maintained on $1\frac{1}{2}$ grains of digitalis folia every day thereafter. An electrocardiogram (Fig. 1, F, Lead III), taken on March 5, 1935, showed A-V block. The atrial rate varied from 164 to 187, and there was a slight degree of A-V block of the Wenckebach type, varying from 6:5 to 23:22, and less. The curves after digitalization were the only ones over a long period that showed any block; all curves taken during subsequent attacks have shown 1:1 A-V conduction.

CASE 7.—C. B., a white man, aged 50 years, John Sealy Hospital No. 48378, was admitted June 20, 1935, with the symptoms and signs of congestive heart failure of a year's duration. The blood pressure was 110/70; pulsus alternans was present. Numerous electrocardiograms, taken from June 27 to July 2, showed atrial tachycardia; the atrial rate varied from 150 to 186. In all the tracings there is 2:1 A-V block (see Fig. 1, G, Lead I). Note that the cycle which contains the QRS complex is shorter. Digitalization was begun on the day after admission and maintained during his hospital stay, without effect on the cardiac mechanism.

He continued to lose ground, and died on July 5, 1935. Necropsy showed coronary arteriosclerosis. The heart weighed 450 grams. He also had hemorrhagic pericarditis, pleuritis, syphilitic leptomeningitis, and hypostatic pneumonia.

CASE 8.—H. P., a white man, aged 53 years, John Sealy Hospital No. 51712, was admitted June 3, 1936, with congestive heart failure which had been present for three months. Anginal pain had been present for three weeks. Electrocardiograms (Fig. 1, H, Lead II) taken before admission, on May 19, 1936, had shown atrial tachycardia, a rate of 200 to 203, and 4:3 and 3:2 block. The next day the atrial rate was 150, with 1:1 conduction. On June 7, $10\frac{1}{2}$ grains of digitalis were given and produced vomiting. The following day mercururin was given, and, the day after this, atrial tachycardia was present with an atrial rate of 182 per minute, but without A-V block. The next day, June 10, he had sinus rhythm at a rate of 128 per minute. The patient died June 14, his eleventh hospital day. Necropsy showed syphilitic aortitis. The heart weighed 480 grams. There was a thrombus in the right auricular appendage, and multiple pulmonary infarcts were found.

CASE 9.—J. G., a colored man, aged 60 years, John Sealy Hospital No. 44449, was admitted June 29, 1936, with congestive heart failure. He had been in the hospital several times in the preceding seven years with similar symptoms and signs, and hypertension as high as 200/130. The blood pressure at this time was 130/100. For several years he had been maintained on digitalis at intervals. Previous electrocardiograms had shown, among other abnormalities, prolonged A-V conduction time. Electrocardiograms (Fig. 1, I, Lead I), in the morning of July 1, showed an atrial rate of 143, with 8:7 and 3:2 A-V block and Wenckebach periods. In the afternoon the atrial rate was 120 per minute, without block. Subsequent tracings showed sinus rhythm. He gradually improved on digitalis and theocalcin and was discharged Aug. 28, 1936.

CASE 10.—F. M., a white man, aged 56 years, John Sealy Hospital No. 45030, was admitted Aug. 24, 1936, with congestive heart failure due to hypertension and arteriosclerotic heart disease. He had had the anginal syndrome since 1933, and three days after admission he developed pulmonary infarction associated with jaundice. On August 28 he was started on digitalis in a dose of $1\frac{1}{2}$ grains three times a day, and this was continued until September 10, when the dosage was reduced to one tablet daily. On September 12, electrocardiograms (Fig. 1, J, Lead I) revealed atrial tachycardia with an atrial rate of 179 per minute and 2:1 A-V block. Note the shortening of the cycle containing the ventricular beat. On September 11 he suffered myocardial infarction, which caused his death on September 14. At necropsy his heart weighed 580 grams; infarction of the myocardium was present, with mural thrombosis associated with multiple infarcts of the lungs, spleen, and brain.

CASE 11.—C. D., a colored man, aged 36 years, John Sealy Hospital No. 52195, was admitted Nov. 20, 1930, with congestive heart failure that had been present for five months. The blood pressure was 160/120, and the physical signs were those of myocardial failure. On December 13 he was given $19\frac{1}{2}$ grains of digitalis by mouth, and the next day electrocardiograms showed paroxysmal atrial tachycardia; the rate was 169 per minute, with 1:1 A-V conduction. On December 15, 23 grains of quinidine were given, and an electrocardiogram (Fig. 2, A, Lead II), on December 16, showed that the tachycardia continued, with the atrial rate varying from 190 to 218, but now with 5:4 and 3:2 Wenckebach A-V block. Note that when the block is present, the cycle that contains the ventricular beat is much shorter. The following day there was sinus tachycardia with a rate of 136 per minute. The patient died Jan 6, 1937, and necropsy was not obtained.

CASE 12.—F. M., a white man, aged 48 years, John Sealy Hospital No. 37597, was admitted Feb. 5, 1938. Congestive heart failure had been present for one month before admission. The previous year the patient had had a gastrointestinal hemorrhage, and anemia persisted. The blood pressure was 218/134, and uremia was also present. Digitalis had been given for one week before admission to the hospital, and was continued at a rate of $1\frac{1}{2}$ grains daily. Electrocardiograms (Fig. 2, B, Lead II), on the day of admission, showed an atrial rate of 200 per minute, with 4:3, 5:4 Wenckebach block. Note the progressive aberration of QRS complexes. After 9 grains of quinidine on February 6, and again on February 7, sinus tachycardia was recorded at a rate of 105 per minute. Nitrogen retention was progressive; papilledema developed, and the patient died of uremia on March 20, 1938.

CASE 13.—J. R., a colored woman, aged 53 years, John Sealy Hospital No. 57901, was admitted Feb. 24, 1938, with congestive heart failure which had been present for one month. She complained also of diarrhea, greenish vision, and vomiting. Before admission she had been given tincture of digitalis in a dose of 60 drops daily for nine days. To this medication had been added powdered digitalis leaf in a dose of $1\frac{1}{2}$ grains three times daily. No digitalis was administered in the hospital

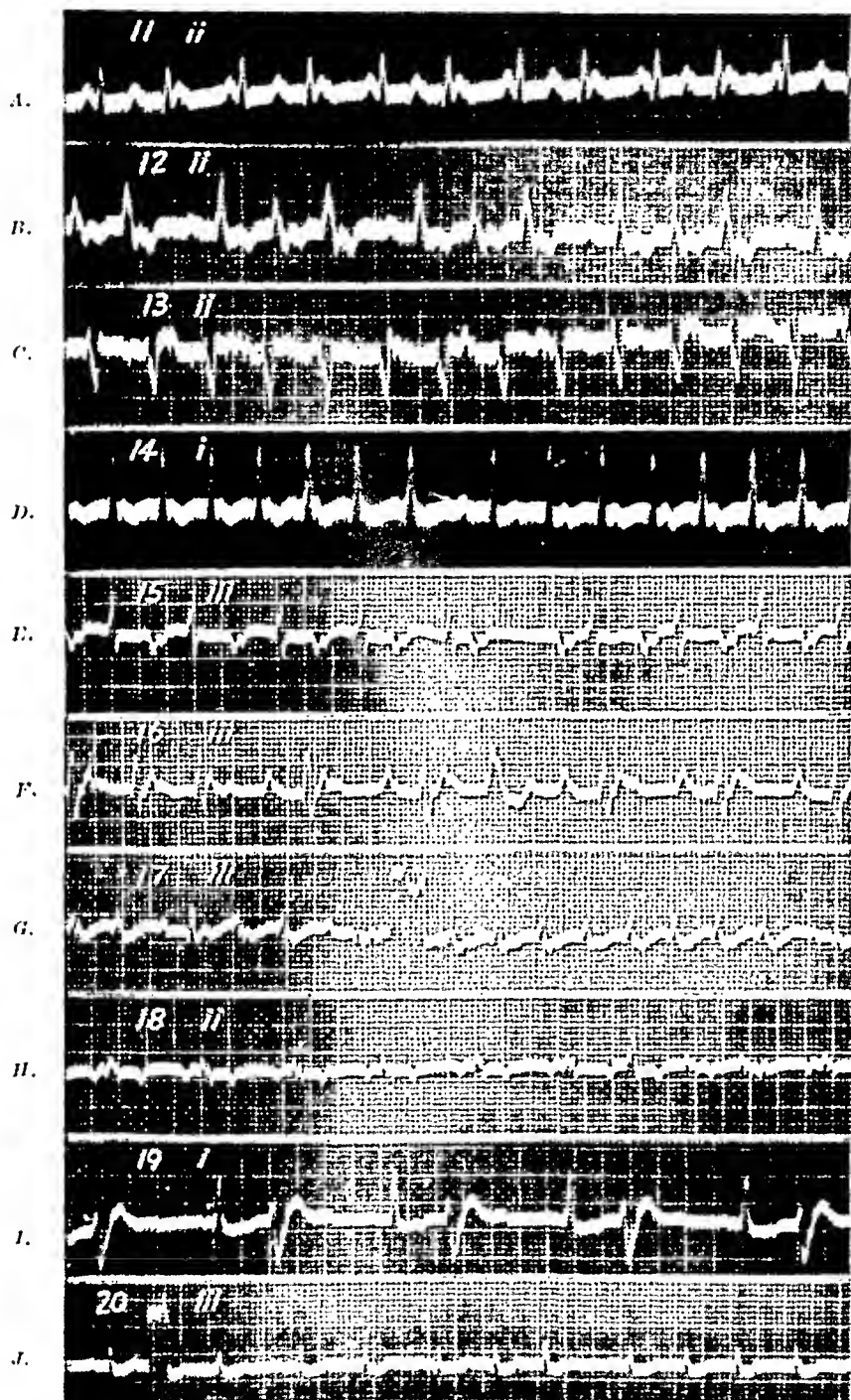


FIG. 2.

because of the obvious previous overdosage. Electrocardiograms (Fig. 2, C, Lead II), taken on admission, showed paroxysmal tachycardia of nodal origin, with a rate of 165 per minute. P waves could be made out, showing an independent atrial tachycardia of 125 per minute, with complete A-V dissociation. By March 1, the rhythm was sinus tachycardia, with delayed A-V conduction.

CASE 14.—K. L., a white man, aged 45 years, John Sealy Hospital No. 57248, was admitted March 7, 1939, with congestive heart failure. The blood pressure was 252/168. A lumbar sympathectomy had been performed fourteen months previously because of this marked hypertension, but very little benefit had resulted. In the five days before admission, the patient had taken 15 $1\frac{1}{2}$ -grain tablets of digitalis. On March 13, 2.5 mg. of digoxin were given intravenously, and on March 14, it was found that atrial fibrillation had developed. On March 17, 18, and 19, $1\frac{1}{2}$ -grain doses of digitalis were given twice daily. Electrocardiograms (Fig. 2, D, Lead I), on March 20, showed paroxysmal atrial tachycardia, with an atrial rate of 182 per minute; 8:7 and 7:6 A-V block was present. On March 22, digitalis was begun again; paroxysmal tachycardia recurred with an atrial rate of 193, with rare dropped ventricular beats. During this time, nitrogen retention had progressively increased, and the patient died, on March 29, of uremia. At necropsy the heart weighed 670 grams and there was marked nephrosclerosis. A few atheromatous plaques were noted in the aorta.

CASE 15.—A D., a white girl, aged 14 years, John Sealy Hospital No. 66298, was admitted April 17, 1940. For four years she had been bothered by attacks of dyspnea which was associated with tachycardia, vertigo, and pain in the chest. The blood pressure was 78/56, and the heart rate was 188 per minute. Electrocardiograms showed that the atrial rate, on April 17, was 158 to 188; on April 18, 187 to 190; on April 19, 130; and on April 22, 120. Quinidine in a dose of 5 grains was given four times daily on April 19 and April 21. On April 19, carotid sinus pressure caused one dropped beat. On April 24 and 25, $1\frac{1}{2}$ grains of digitalis were given three times daily. On April 26 and 27, digitalis was given twice daily and once daily thereafter. In electrocardiograms (Fig. 2, E, Lead III), taken April 26, the atrial rate was 125, with occasional dropped beats and Wenckebach periods. On April 30 the rate was 115, and there were frequent blocked beats. The atrial rate showed marked variation. The treatment caused a slowing in the atrial rate, although the ectopic pacemaker persisted during the whole period. On May 16 the patient had a sudden attack of extreme tachycardia, with a rate of 250 per minute; this was probably also ectopic, as the others had been for four years. No measures resulted in improvement. Necropsy showed a heart which weighed 430 grams and was markedly dilated and hypertrophied. There was a patent ductus arteriosus which measured 1 mm. in diameter. The aorta was very small, measuring only 50 mm. in circumference at the ring. Congenital hypoplasia of the aorta was considered to be the primary cardiac disease.

CASE 16.—D. E., a colored man, aged 45 years, John Sealy Hospital No. 67100, was admitted Sept. 17, 1940. This patient had been in the hospital twice previously in 1940, with congestive heart failure due to hypertensive heart disease. The blood pressure was 180/110. Pulsus alternans and gallop rhythm were present, and mild congestive failure was evident. The patient had been maintained on $1\frac{1}{2}$ grains of digitalis leaf daily since his first hospital admission on June 7, 1940; on July 3 bigeminy had been noted, probably due to digitalis overdosage. When first seen on September 17, electrocardiograms showed an atrial rate of 152 per minute with 1:1 A-V conduction. Deep respiration slowed the atrial rate from 150 to 144 and there was A-V block varying between 2:1 and 5:4. Carotid sinus pressure produced 2:1 to 6:5 block, with frequent ventricular escapes, as shown in the electrocardiograms (Fig. 2, F, Lead III). Quinidine was administered, and the atrial rate

slowed from 158 to 143, with variable block, sometimes as high as 3:1, with ventricular escape. Cycles containing ventricular beats measured 0.40 second and blocked cycles measured 0.45 second. Deep respiration and carotid sinus pressure produced A-V block, the grade of which was increased after quinidine administration. A few hours after the use of quinidine, the paroxysmal tachycardia disappeared.

CASE 17.—R. Z., a white woman, aged 63 years, John Sealy Hospital No. 67926, was admitted Aug. 15, 1940, in a semicomatose condition. She had been weak for about four days, and her relatives stated that she had had dyspnea and edema, nocturnal coughing, orthopnea, and hypertension, for two years. The blood pressure was 190/80, and she had Cheyne-Stokes respiration, but there was no evidence of congestive heart failure. On August 28 an attack of paroxysmal tachycardia, with an atrial rate of 162, was recorded. It stopped spontaneously. On September 4 another attack was recorded, with an atrial rate varying from 188 to 250, and with aberrant QRS complexes. This attack was stopped by 3 grains of quinidine every hour for ten doses. On other occasions there were frequent atrial premature beats. On November 6 she had another paroxysm, and electrocardiograms (Fig. 2, G, Lead III) showed an atrial rate of 160 to 169, with a Wenckebach period type of A-V block varying from 4:3 to 11:10, and less. Death occurred Nov. 17, 1940. The final diagnosis was generalized arteriosclerosis, with particular involvement of the coronary and intracranial arteries.

CASE 18.—T. R., a white man, aged 49 years, John Sealy Hospital No. 66787, was admitted Oct. 15, 1940. Congestive heart failure was present and had been present on previous occasions. The blood pressure was 128/100, gallop rhythm was present, and pulmonary congestion was marked. Digitalis (1½-grain tablets) was given three times a day for four days, from November 22 to November 25, then one tablet daily until November 27. Beginning November 28, three 1½ grain doses were again given daily, until December 8. On December 1, 2 c.c. of mercupurin were injected intravenously and resulted in considerable diuresis; on December 2 atrial fibrillation developed. Eighteen grains of quinidine were given that day and stopped the fibrillation. The following day, December 3, electrocardiograms (Fig. 2, H, Lead II) showed atrial tachycardia with an atrial rate varying from 150 to 188 per minute, and block, varying from 2:1 to 9:8, of the Wenckebach type. Note here also the variation of the cycle length. The patient died December 14, and necropsy showed a heart weighing 600 grams, with slight coronary arteriosclerosis. There were thrombi in both ventricles and in the right atrium, and there were multiple pulmonary infarcts. Nephrosclerosis was present, and there was, of course, chronic congestion in the viscera.

CASE 19.—V. N., a colored woman, aged 38 years, John Sealy Hospital No. 70439, was admitted April 9, 1941. She showed marked congestive heart failure which had been present for about two months. At home she had taken some small brown pills of uncertain nature. The blood pressure was 200/20 and the other physical signs were those of syphilitic aortic regurgitation. Electrocardiograms, on admission, showed sinus tachycardia, left axis deviation, depression of the S-T segments in Leads I and II, and negative T waves in Leads I and IV F. Digoxin (1 mg.) was given intravenously, and fifteen minutes later she vomited and had bigeminy and trigeminy. Electrocardiograms (Fig. 2, I, Lead I), taken at this time, showed an atrial rate of 190 per minute, with 4:1 A-V block and frequent ventricular escape, usually giving bigeminy. Death occurred a few hours later, and necropsy showed typical syphilitic aortitis and aortic regurgitation. The heart weighed 430 grams.

CASE 20.—J. W., a white man, aged 81 years, John Sealy Hospital No. 69078, was admitted March 17, 1941, because of prostatic disease. Prostatic resection was done March 26. On April 7 the patient had a short attack of paroxysmal dyspnea, which recurred on April 16. Electrocardiograms, the next day, showed short runs of paroxysmal atrial tachycardia. Digitalization was begun at this time, with $13\frac{1}{2}$ grains of the powdered leaf of digitalis the first day, and maintenance doses of $1\frac{1}{2}$ grains daily, afterwards. Electrocardiograms (Fig. 2, J, Lead III), on April 28, showed paroxysmal tachycardia with an atrial rate of 179 per minute; 6:5, 4:3, and 3:2 A-V block of the Wenckebach type was present. Quinidine, which was given on this day and on April 29, terminated the paroxysm. Electrocardiograms both before and after this attack showed frequent atrial premature beats.

CASE 21.—G. S., a colored woman, aged 24 years, John Sealy Hospital No. 71436, was admitted June 23, 1941. She had had paroxysms of tachycardia since childhood. At the time of her admission she was seven months pregnant, and had had frequent paroxysms in the preceding two months. The attack which brought her to the hospital had lasted for six days, and had been associated with difficulty in hearing, dyspnea, edema, and precordial pain radiating to the right shoulder. She had had three previous miscarriages. She had anemia, with a hemoglobin of 55 per cent. The blood pressure was 120/75. The heart was normal in size and no cardiac lesion could be demonstrated. When first seen, the heart rate was 220 per minute, the beating regular, and the rhythm was not affected by carotid sinus pressure. Eight cubic centimeters of cedilanid, equivalent to 1.6 mg., was injected intravenously, and three minutes later there was a sudden slowing of the heart rate to 120 per minute. Tachycardia recurred thirty-six hours later, and at this time 8 c.c. more of cedilanid were injected. Immediately afterwards, electrocardiograms (Fig. 3, A, Lead I) showed an atrial rate of 118 per minute, with, roughly, 7:5 A-V block. The form of the P waves indicated that the ectopic focus was still effective. During the paroxysms of tachycardia, QRS aberration was present. At the termination of the paroxysm, gradual, stepwise return of intraventricular conduction to normal could be demonstrated. In later paroxysms, digitalis extract (Upjohn, 5 cat units in 10 c.c.), intravenously, stopped the attack immediately. Prostigmine was effective on one occasion, although at several other times it was not. Magnesium sulfate by vein was ineffective. The paroxysms were best controlled by the regular administration of quinidine, but even then occasional short paroxysms occurred.

CASE 22.—H. J., a white woman, aged 70 years, John Sealy Hospital No. 46412, was admitted July 4, 1941. She had had a left-sided hemiplegia in 1934, at which time her blood pressure was 190/140. Since then she had had several syncopal attacks, and for several months she had had moderate congestive heart failure. On admission, the venous pressure was 17 cm. of water, and there were evidences of fluid in both pleural sacs. The blood pressure at this time was 130/84. On July 5 and 6, a transudate was removed from the left pleura by thoracentesis. On both July 6 and 7, Cheyne-Stokes respiration was noticed, and $7\frac{1}{2}$ grains of aminophylline were given by vein for relief. On July 6, digitalis folia ($1\frac{1}{2}$ grains three times a day) was begun. The next day, tachycardia was present and the recorded rates varied from 207 to 255; when the rate was 207 per minute, there was 1:1 A-V conduction (Lead I, Fig. 3, B); when the rate was 222 per minute, the A-V conduction was 3:2 block of the Wenckebach type. When the rate was as high as 255 per minute, A-V conduction was only 2:1. Intraventricular conduction was also defective. On July 8 there was shifting of the pacemaker, with defective intraventricular conduction. It should be noted that before the paroxysmal tachycardia there were frequent atrial premature beats. The atrial tachycardia ceased after the administration of 5 grains of quinidine every hour for four doses.

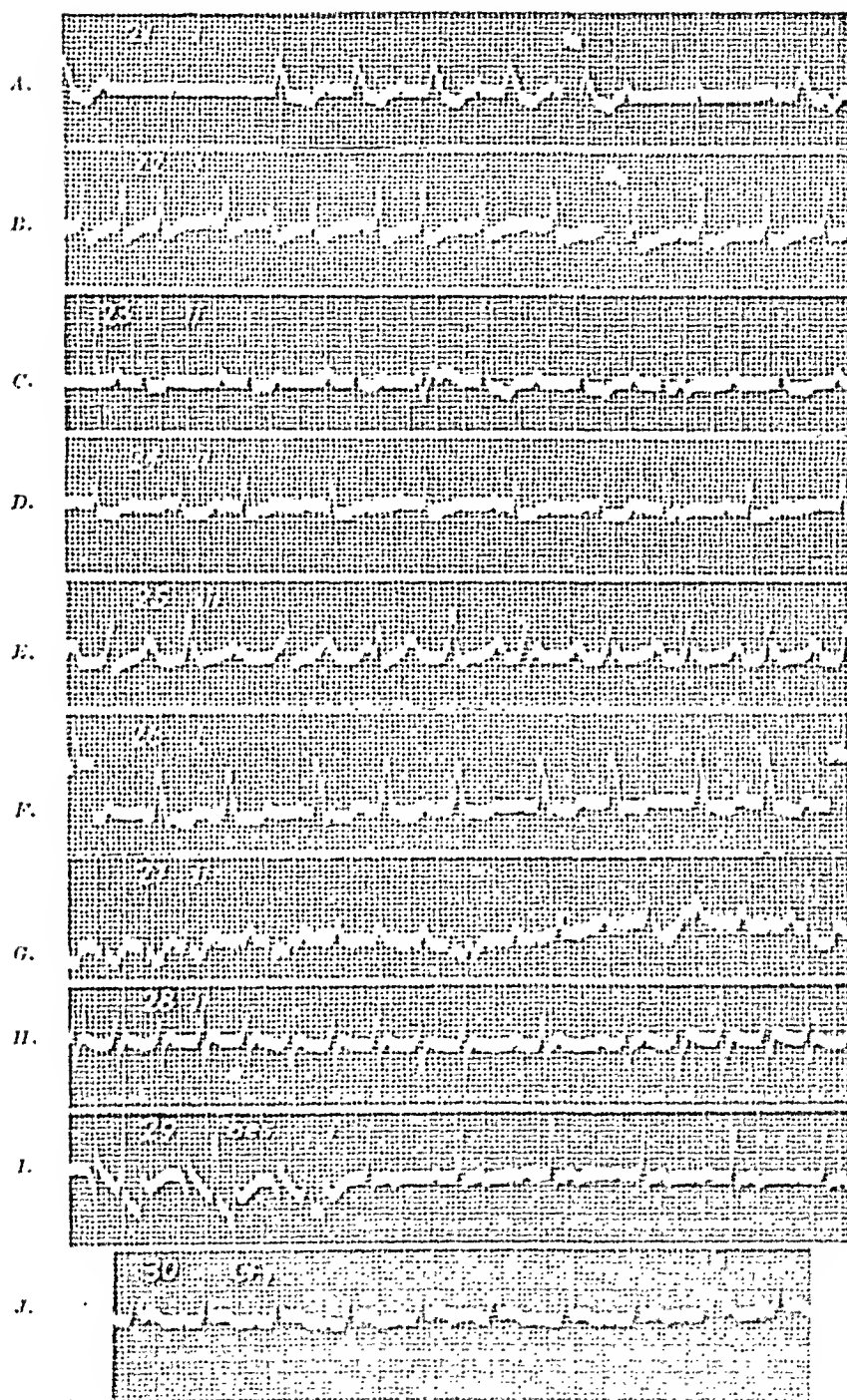


FIG. 3.

On the fifth hospital day the temperature rose, the dyspnea became more marked, and fluid reaccumulated in the pleural spaces; the patient became worse rapidly, and died on the seventh day. Necropsy showed that the heart weighed 365 grams. Purulent pericarditis, bronchopneumonia, peritonitis, and mild chronic passive congestion of all organs were found. There was an acute infectious process in the bladder and ureters, and encephalomalacia.

CASE 23.—W. W., a colored man, aged 38 years, John Sealy Outpatient Clinic No. 49248, was admitted Aug. 2, 1941. He had been seen in the Outpatient Department, three days before, with congestive heart failure which, according to his story, had been present four or five weeks. The blood pressure at this time was 160/130. There were cardiac enlargement, gallop rhythm, engorgement of the liver, and dependent edema. He had a history of a chancre in 1926. In the three-day interval he had taken sixteen tablets, of $1\frac{1}{2}$ grain each, of digitalis leaf. Electrocardiograms, taken August 2, showed paroxysmal tachycardia with an atrial rate of 196 per minute and 1:1 A-V conduction. One milligram of prostigmine was given intramuscularly, and, after about ten minutes, there was transient slowing. Atrial tachycardia soon recurred; however, the auricular rate was only 182 per minute and there was 2:1 A-V block. Carotid sinus pressure had had no effect before, but at this time carotid sinus pressure and deep respiration increased the A-V conduction disturbance. Fig. 3, C, Lead II, shows A-V block of 2:1, and, in some parts, of 3:1. The atrial rate remained slow, and was from 156 to 176. During the period of block there were many nodal escapes and transient intraventricular conduction defects.

CASE 24.—P. J., a colored man, aged 76 years, John Sealy Hospital No. 78053, was admitted March 1, 1943, because of congestive heart failure. Dyspnea on exertion had been present for two years and gradually increasing edema had been noted for twelve months. For the preceding eighteen days these symptoms had been much worse. No medication had been administered.

The blood pressure was 200/90; the heart was conspicuously enlarged, and there were the usual evidences of chronic passive congestion of moderate grade. Atrial fibrillation was present and was shown in all electrocardiograms taken up to and including one on March 16.

Eighteen grains of powdered digitalis leaf were given by March 5, and after this date $1\frac{1}{2}$ grains were given daily. Quinidine (3 grains three times a day) was given from March 12 to 20, at which time the dosage was increased to 5 grains three times a day. An electrocardiogram, taken March 20, showed atrial tachycardia, with an atrial rate of 166 to 171 per minute and 2:1 and 3:2 A-V block. The tracing taken March 22 showed an atrial rate of 214 per minute, with 2:1 A-V block. An hour later the auricular rate had dropped to 162, and there was 1:1 conduction. At this time 1 mg. of prostigmine was injected intramuscularly, and, with an atrial rate of 171 to 179, varying A-V block developed, either 2:1 or 3:2 of the Wenckebach type (Fig. 3, D, Lead II). The auricular rate was 176 on March 26, with 2:1 A-V block; after this date there was sinus rhythm with frequent auricular premature beats. Improvement was such that he was discharged April 4, 1943.

CASE 25.—W. L., a colored man, aged 74 years, John Sealy Hospital No. 73536, was admitted Nov. 18, 1941, because of genitourinary symptoms resulting from prostatic hypertrophy and a urethral stricture. His history further revealed nocturnal dyspnea. His blood pressure was found to be 200/140. Cheyne-Stokes respiration was present, as were the usual evidences of congestive heart failure. The Cheyne-Stokes respiration ceased after the administration of $7\frac{1}{2}$ grains of aminophylline intramuscularly. Aminophylline was continued by mouth in a dose of 3 grains four times a day. On December 10, digitalis folia was begun in doses of $1\frac{1}{2}$ grains three times a day, but only five doses were given. On December 12 it was found that the heartbeat was irregular, with an apical rate of 118 per minute. Electro-

cardiograms showed atrial tachycardia with an atrial rate varying from 167 to 196 per minute. At the lower rate there was 1:1 conduction, or, at most, 12:11 A-V block. At the higher rate there was 2:1 A-V block. On December 12, 25 grains of quinidine were given, and, on December 13, electrocardiograms (Lead III, Fig. 3, E) showed an auricular rate of 182 per minute with A-V block varying from 4:3 and 3:2 to 2:1. The patient died December 14 and necropsy showed that the heart weighed 590 grams. There were moderate coronary arteriosclerosis, marked nephrosclerosis, pneumonia, and generalized chronic passive congestion.

CASE 26.—E. W., a white woman, aged 65 years, John Sealy Hospital No. 74287, entered Jan. 5, 1942, because of paroxysmal nocturnal dyspnea and substernal pain. The blood pressure was 180/120 and the clinical signs were those of left ventricular failure. The electrocardiogram (Lead I, Fig. 3, F), taken on admission, showed an atrial rate of 260, with A-V block alternating between 2:1 and 3:1. Bundle branch block was also present. The tachycardia disappeared spontaneously, and later electrocardiograms showed frequent atrial premature beats. The bundle branch block persisted. Subsequent use of digitalis and coramine was followed by improvement.

CASE 27.—F. G., a colored man, aged 59 years, John Sealy Hospital No. 10629, was admitted Jan. 20, 1942. He had hypertensive and arteriosclerotic heart disease and had had dyspnea for six years. Substernal pain had been present for eight months and had been noted to increase during paroxysmal tachycardia. Electrocardiograms taken a year previously had shown atrial fibrillation, and the more recent ones showed reversion to sinus tachycardia. The blood pressure on admission was 136/96, and the physical signs were those of mild congestive heart failure. For three months the patient had been taking 3 grains of digitalis leaf daily. On the day of admission the electrocardiogram showed paroxysmal atrial tachycardia with an auricular rate of 214 per minute and 1:1 A-V conduction. The next day, January 21, electrocardiograms revealed an auricular rate of 200, with 2:1 A-V block. Carotid sinus pressure produced 3:1 and 4:1 A-V block, with occasional ventricular escape (Fig. 3, G, Lead II). Sitting up doubled the heart rate, and reclining caused it to drop back. Electrocardiograms taken nine months later showed that auricular fibrillation had appeared again.

CASE 28.—A. H., a colored woman, aged 46 years, John Sealy Hospital No. 19506, was admitted Jan. 15, 1942. Her blood pressure was known to have been elevated since 1926. She had been under treatment with digitalis for congestive heart failure, for four months before admission. Edema had been present for three weeks, but she had been taking digitalis only as she thought she needed it. When seen on this admission, the blood pressure was 250/160. The heart was markedly enlarged and there was massive edema. The blood nonprotein nitrogen level was elevated; the serum albumin was 3.44 per cent, and the globulin was 6.2 per cent. She had a rectal stricture caused by lymphogranuloma inguinale.

The day of admission, January 15, electrocardiograms showed auricular fibrillation. The next day, 1½ grain digitalis pills were administered three times a day, and this was continued during her hospital stay. On January 18 electrocardiograms showed paroxysmal tachycardia with an atrial rate of 194 per minute and 2:1 and 3:2 block. On January 20 sinus rhythm was present, with a rate of 133 per minute. On January 25 electrocardiograms (Lead II, Fig. 3, H) showed tachycardia with the auricular rate varying from 184 to 197 and a variable degree of A-V block—as little as 13:12 and as high as 2:1. There was also aberration of the QRS complexes, and the cycles containing the ventricular beats were shorter than those that were blocked. She died of uremia January 26.

At necropsy the heart weighed 515 grams and showed pericarditis. There were nephrosclerosis, bronchopneumonia, cerebral thrombosis, several pulmonary infarcts,

and chronic passive congestion. Lymphogranuloma inguinale, with rectal stricture, was found.

CASE 29.—A J., a colored man, aged 42 years, John Sealy Hospital No. 74824, was admitted Feb. 17, 1942, with congestive heart failure. He had hypertensive heart disease, with a blood pressure of 188/108. In addition to this he had renal insufficiency. The blood nonprotein nitrogen rose to 185 mg. per cent on March 12, a week before his death. It was learned that he had taken digitalis during January, but the exact amount was not known. Beginning February 18, the day after admission, he was given a $1\frac{1}{2}$ -grain digitalis tablet three times a day until February 23; the next day $1\frac{1}{2}$ grains daily were given, and this dose was continued until his death. Electrocardiograms, on February 17 and 19, showed sinus tachycardia. On February 21, electrocardiograms (Fig. 3, I, Lead I, preceded by a short strip of an esophageal lead) showed an auricular rate of 179 to 190, with 2:1 A-V block. By February 24, the sinus tachycardia returned; on February 28, there was nodal rhythm, with a rate of 86 and shifting of the pacemaker. In the electrocardiograms (Fig. 3, I) the cycles containing the ventricular beats were 0.32 second, and those without a ventricular beat were 0.335 second. This patient died on March 20 of uremia. At necropsy the weight of the heart was 570 grams, and fibrinous pericarditis, benign nephrosclerosis, and an infarct of the right lung were found. The coronary arteries were not grossly involved.

CASE 30.—C. O., a white man, aged 73 years, John Sealy Hospital No. 44749, was admitted April 17, 1942, semicomatose, with Cheyne-Stokes breathing and a right-sided hemiplegia. The blood pressure was 180/104. The heart was enlarged and there was generalized arteriosclerosis. The signs of congestive failure were not conspicuous; the venous pressure was only 13 cm. of water. On both April 17 and 18 he received 1 mg. of digoxin intravenously, and on April 19 and 20 he received 0.5 mg. In addition, 0.5 Gm. of aminophylline was given by vein on April 18, 19, and 20. On April 18, the record showed atrial tachycardia with an atrial rate of 240 per minute and 2:1 block. Electrocardiograms on April 21 (Fig. 3, J, Lead CF₁) showed an atrial rate of 230 per minute, with 2:1 block. On April 24, sinus rhythm, with a rate of 75 per minute, was recorded. On May 2 electrocardiograms showed atrial flutter, which was controlled by quinidine on May 3 and 4. On May 4 sinus rhythm was recorded; but on May 5 atrial fibrillation was present.

CASE 31.—J. H., a white man, aged 79 years, John Sealy Hospital No. 61445, was admitted June 9, 1941, in a prolonged, persistent attack of tachycardia, with evidences of heart failure. He had been known to have paroxysms over a period of six years. Carotid sinus pressure had usually been without effect, and he had been taking 5 grains of quinidine three times a day. He had benign prostatic hypertrophy, and required frequent catheterization. Eighteen months before he had had a transurethral resection. Most of his preceding attacks had lasted not over two hours. The attack of June 9 had lasted more than twenty-four hours, and had produced dyspnea, pulsus alternans, pulmonary and hepatic congestion, and edema of the lower extremities. The neck veins were distended and there was Cheyne-Stokes breathing. The blood pressure was 128/88. The previous electrocardiograms, over a period of years, showed right bundle branch block with many paroxysms of tachycardia. On June 9, at 11:30 P.M., shortly after admission, he was given 1.2 mg. of cedilanid intramuscularly, and the next morning, at 9 o'clock, he was given 0.4 mg. more. This dose of 0.4 mg. was repeated that evening and again the next day. An electrocardiogram (Lead II, Fig. 4, A upper), with carotid sinus pressure, on June 10, showed atrial tachycardia with an average rate of 162 per minute and varying degrees of A-V block, 6:5 and more, to 6:1, with ventricular escape. On June 13, with the atrial rate at 165, and 1:1 conduction (Fig. 4, A lower, Lead I), there was alternation of cycle length (between 0.315 second and 0.37 second).

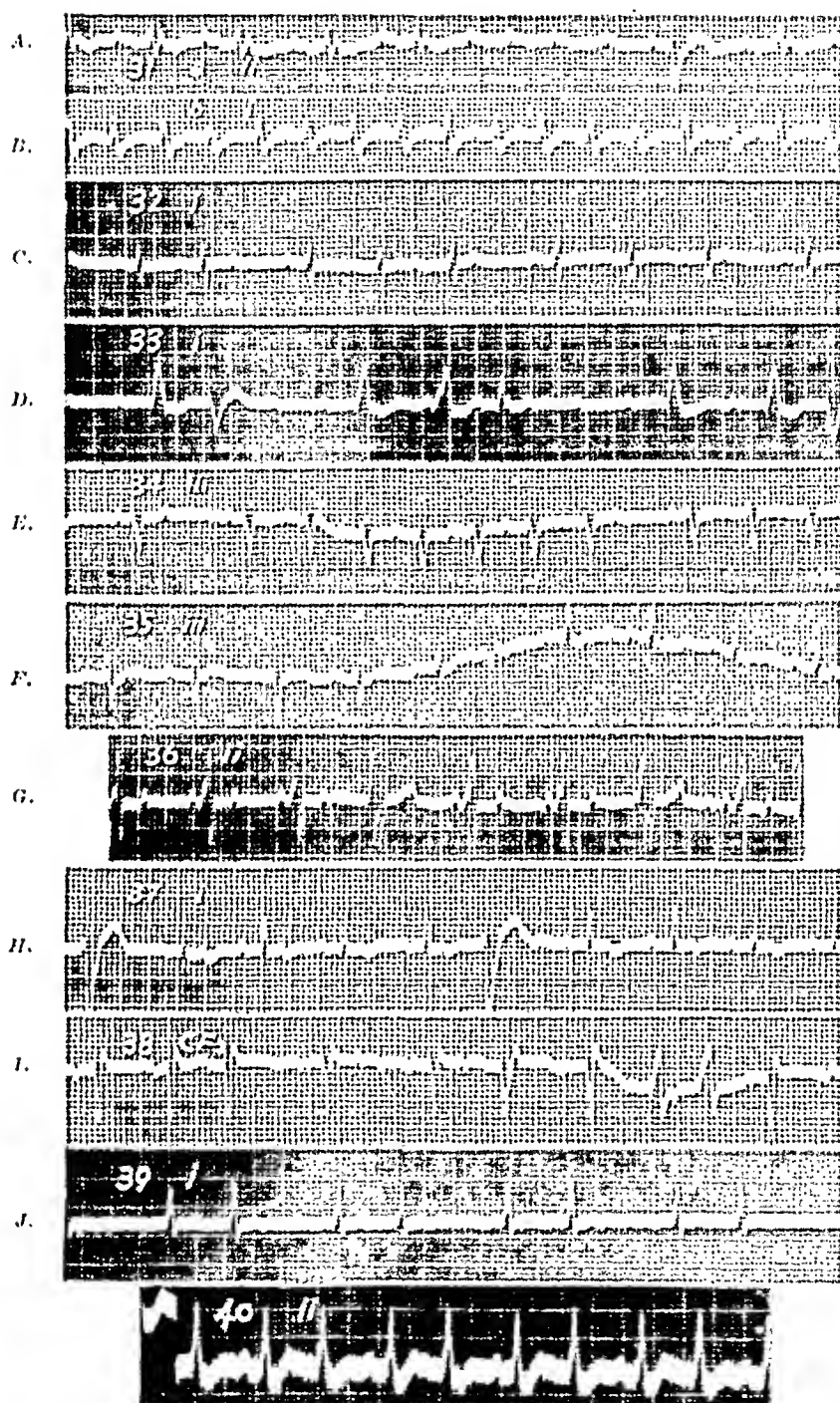


FIG. 1.

Other drugs used were coramine and aminophylline, both by month. Death occurred March 31, 1943, as a result of gangrenous cystitis.

CASE 32.—O. H., a white woman, aged 25 years, John Sealy Hospital No. 76594, was admitted July 2, 1942. This patient had had a fever for four months, edema of her eyes, feet, and legs, and abdominal distention. She was found to have subacute bacterial endocarditis, and it was thought that she also had chronic glomerulonephritis. In addition, there was evidence of congestive heart failure. On July 5, 6, 7, and 8, she was given four tablets of digitalis of $1\frac{1}{2}$ grains each. On July 9 she received two tablets, and, after that, one tablet daily. Sinus rhythm had been present on July 3. On July 9, electrocardiograms (Lead I, Fig. 4, B) showed a short paroxysm of atrial tachycardia; the atrial rate was 150 to 160, with 2:1 and 3:1 A-V block. Subsequent electrocardiograms showed sinus rhythm, with occasional premature atrial beats. In one tracing there was a short paroxysm of auricular fibrillation.

CASE 33.—H. H., a white man, aged 64 years, John Sealy Hospital No. 75738, was admitted June 26, 1942, with congestive heart failure. He had been in the hospital during the preceding month because of congestive heart failure. The blood pressure was 163/124, and there were the usual symptoms and signs of myocardial insufficiency. On June 27, the day after admission, he was given 8 c.c. of digilamid by vein. Digitalization was maintained by the administration of $1\frac{1}{2}$ grains of digitalis leaf twice daily. On July 15, he was given 2 c.c. of mercupurin, which resulted in a satisfactory diuresis. Electrocardiograms had shown prolonged A-V conduction. On July 17, he was found to have paroxysmal atrial tachycardia with an atrial rate of 162. On July 18, the electrocardiogram (Lead I, Fig. 4, C) showed a rate of 156 per minute, with 2:1 block, occasional periods of 4:1 block, and ventricular escape. Bundle branch block was also present. Later electrocardiograms showed again the prolonged P-R interval of 0.24 second. The patient died on July 22. At necropsy the heart weighed 450 grams. There were bilateral pulmonary infarcts, both old and recent. Pleural effusion and bronchopneumonia were present. Myocardial hypertrophy, with fibrosis of the myocardium, was demonstrated microscopically. There were generalized arteriosclerosis, nephrosclerosis, and chronic passive congestion of the viscera.

CASE 34.—M. G., a white man, aged 46 years, John Sealy Hospital No. 77524, was admitted Aug. 27, 1942, because of arteriosclerotic heart disease which had led to symptoms of congestive heart failure for four months. Two days after admission he was given 9 grains of digitalis folia, and the following day he was given 6 grains more. This latter dose was repeated on August 31 and September 1. Beginning September 2, a daily dose of $1\frac{1}{2}$ grains was used. On August 28, the day after admission, the electrocardiograms showed sinus rhythm, with a rate of 79 per minute. By August 30, however, the electrocardiogram (Lead III, Fig. 4, D) showed atrial tachycardia with an auricular rate of 150 per minute and A-V block of 3:2, 6:5, and less. Atrial premature beats had been seen on previous tracings, and, on August 31, atrial fibrillation developed. This persisted until October 21, at which time sinus rhythm appeared.

CASE 35.—D. N., a white man, aged 53 years, John Sealy Hospital No. 37379, was admitted Sept. 8, 1942. He had been seen in 1932, when he was suffering from hypertensive encephalopathy; the blood pressure at that time was 190/110. At this admission he complained of severe substernal pain of three days' duration, associated with dyspnea for one day. Examination showed that the blood pressure was 220/120, and there were the usual signs of congestive heart failure. The patient had been given eleven tablets of digitalis folia, of $1\frac{1}{2}$ grains each, during the four days preceding admission. The day of admission, September 8, he was given two injections of digilamid, 3 cat units each, six hours apart. The following day, an electrocardio-

gram was taken, and the chest leads showed evidence of anterior myocardial infarction. It also showed (Fig. 4, E, Lead III) an atrial rate of 193 to 207 per minute, and 2:1 A-V block. Occasionally, the A-V block was only 3:2, and of the Wenckebach type. There was aberration of the QRS complexes. The cycle which contained the ventricular beat was 0.29 second, and that which had a blocked auricular beat was 0.31 second. Digitalis was stopped and quinidine was administered. The following day sinus rhythm was re-established.

CASE 36.—J. M., a colored man, aged 51 years, John Sealy Hospital No. 16217, was admitted Oct. 21, 1942. This man had had congestive failure since 1940. He had hypertensive and arteriosclerotic heart disease, with a blood pressure of 220/110. He had been taking digitalis irregularly, usually one and two tablets on alternate days. On admission, he had bigeminy and presented the usual evidence of congestive heart failure. On October 25 he had severe epigastric pain, and serial electrocardiograms showed evidence of acute myocardial infarction. A pericardial friction rub was heard the next day. Since the patient was already overdigitalized, mereupurin was employed to control his edema, and, on October 26, 28, and 30, 2 c.c. of mereupurin were injected intravenously. On October 26, electrocardiograms (Lead II, Fig. 4, F) showed atrial tachycardia, with rates varying from 171 to 193, and A-V block ranging from 3:1 to 3:2 to 2:1, often with QRS aberration. The atrial cycles containing a ventricular beat measured 0.31 second. Those containing the blocked atrial beat measured 0.35 second. On October 27 electrocardiograms showed auricular tachycardia at the rate of 115 per minute, but with the pacemaker in the ectopic focus recorded on October 26. This was stopped by carotid sinus pressure. On October 30 the same ectopic focus produced a tachycardia at the rate of 150 per minute, with only occasional dropped ventricular beats. This patient responded poorly to treatment, gradually became worse over a period of two months, and died Jan. 1, 1943. The necropsy showed great cardiac hypertrophy and dilatation, with coronary arteriosclerosis. There were renal arteriolar changes and chronic passive congestion of the viscera.

CASE 37.—L. H., a white woman, aged 61 years, John Sealy Hospital No. 80555, was admitted March 19, 1943, with symptoms and signs of hypertensive heart disease. Congestive failure had appeared four years previously but had been controlled by the daily use of digitalis; however, the dosage was rather irregular, and had been occasionally as much as 5 grains daily. Two weeks before admission, there had been an exacerbation of her dyspnea. The blood pressure was found to be 280/180. The heart was enlarged to the anterior axillary line, and there were the usual manifestations of passive congestion.

Beginning March 20, 1943, 7½ grains of aminophylline were given daily, intramuscularly, and two 1½-grain tablets of digitalis were given March 20, 21, 22, and 23. On March 19, electrocardiograms showed sinus rhythm and a rate of 100 per minute. On March 22, she had auricular tachycardia, with an auricular rate of 207 to 214 and 2:1 A-V block (Fig. 4, G, Lead I). The next day she again had sinus tachycardia, with a rate of 193 per minute; only one short run of auricular ectopic beats appeared on the record.

CASE 38.—E. S., a colored woman, aged 65 years, John Sealy Hospital No. 75227, entered the hospital March 25, 1943, because of dyspnea and cough. She had been hospitalized twice in 1942 because of congestive heart failure due to hypertensive and arteriosclerotic heart disease. Numerous electrocardiograms, since March 22, 1942, had shown auricular premature beats, and, for a short period in August, 1942, auricular fibrillation had been present. Since Sept. 27, 1942, she had been attending the Outpatient Department intermittently, and had been maintained on 1½ grains of digitalis daily. Two weeks before admission, her own physician increased this dosage to 1½ grains three times a day. Palpitation and vomiting were noted three days before admission.

The blood pressure was 156/100. The heart was enlarged, as was the liver. The cardiac rhythm was irregular. Electrocardiograms, on March 26, 1943, showed many short runs of auricular premature beats. On March 29 and 31, the tracings showed auricular flutter. By April 1, the flutter had been replaced by sinus rhythm, with many auricular premature beats. April 5 the same mechanism persisted, with irregular A-V block (Fig. 4, H, Lead CF₂).

The flutter was terminated March 31 by quinidine (eight doses of 5 grains each). On April 1 only 5 grains of quinidine were used; but from April 2 to 5, 5 grains were given three times a day. On April 3 digitalis was begun in doses of 1½ grains daily.

CASE 39.—J. M., a colored man, aged 48 years, entered Charity Hospital Feb. 14, 1931, in an extreme stage of congestive heart failure. He had a cough and hemoptysis which suggested pulmonary infarction. Dizziness and tightness of the chest had been present for some time. He had been in the hospital a month previously with the same symptoms. He had a hard chancre in 1900. Conspicuous orthopnea and generalized anasarca were noted. He presented evidence of cardiac enlargement, and a striking gallop rhythm was heard. The blood pressure was 180/100. Râles were present at the bases of the lungs. There was some ascites. The edge of the liver could not be felt. The extremities were edematous. The urine was of low specific gravity (1.008), and the output was low. The blood nonprotein nitrogen was elevated to 60 mg. per cent. The blood serologic reactions were positive. On Feb. 14, 1931, he was given, intravenously, 5 c.c. of digalen at 5:45 P.M. February 15, he received 3 c.c. more of digalen intravenously. Electrocardiograms taken February 16 showed paroxysmal atrial tachycardia, with 3:2 block and a rate of 154 per minute (Fig. 4, I, Lead I). Tincture of digitalis in a dose of 30 minims was started February 21. The patient continued to grow worse and died March 4, 1931. No autopsy was done.

CASE 40.—M. C., a Negress, aged 22 years, entered Charity Hospital Jan. 26, 1928, with congestive failure and paralysis. Her symptoms began at the end of her pregnancy, three weeks before admission, when she had noticed attacks of severe weakness and dizziness. At the age of 20 years she had had severe malaria which lasted for several months. She had had mild attacks of tonsillitis, and occasionally aching in the shoulders, but no typical rheumatic fever. Her marital and family histories were negative. She was orthopneic, her tonsils were inflamed, her thyroid gland was enlarged, her heart was enlarged, and the rate was fast. There was gallop rhythm, and, at times, irregularities of rhythm were noted; her blood pressure was 121/62. The liver and abdomen were negative. The extremities were edematous and there was partial paralysis of the legs. The urine was of low specific gravity (1.005), and contained albumin and granular casts. Electrocardiograms taken on the day of admission showed paroxysmal tachycardia with an atrial rate of 206 to 222 and occasional dropped beats; the block at times was as much as 3:2 (Fig. 4, J, Lead II). According to the record, the patient had apparently received no medication, although she might have received digitalis before she left home. She died on the second hospital day, and no autopsy was done.

ANALYSIS OF ILLUSTRATIVE CLINICAL MATERIAL

Our clinical material has been derived from electrocardiograms taken on 8,800 patients over a period of about twelve years. Included are one hundred two examples of supraventricular paroxysmal tachycardia of varying duration. Study of these curves showed that there was failure of atrioventricular conduction in thirty-eight instances. Two additional cases from Charity Hospital in New Orleans are included. In others the A-V conduction time was relatively prolonged, but these cases were not

included because simple prolongation of the P-R interval in association with paroxysmal tachycardia was not studied further. This study concerns only those cases of paroxysmal tachycardia in which there were definitely dropped ventricular beats.

Race, Sex, Mortality.—Table I shows the insignificant sex and racial distribution, as well as the significant mortality statistics. Death occurred in twenty-two cases (55 per cent) during the period of hospitalization in which paroxysmal tachycardia with block was found. This fact emphasizes the serious prognostic implication of the concomitant presence of A-V block and paroxysmal tachycardia.

TABLE I
SEX, RACE, AND MORTALITY

	WHITE MALE	WHITE FEMALE	COLORED MALE	COLORED FEMALE	TOTAL
LIVED	6	4	6	2	18 (45%)
DIED	7	3	8	4	22 (55%)
TOTAL	13	7	14	6	40 (100%)
	Males 27 (67.5%)		Females 13 (32.5%)		

TABLE II
TYPE OF HEART DISEASE

AGE (DECADE)	NO HEART DISEASE	CONGENITAL	SUBACUTE BACTERIAL ENDOCARDITIS	POST PARTUM	SYPHILITIC	HYPERTENSIVE	ARTERIOSCLEROTIC	HYPERTENSIVE AND ARTERIOSCLEROTIC	TOTAL
10-19		1							1
20-29	2		1	1					4
30-39					1	2			3
40-49						2	2	1	5
50-59								0	0
60-69					1	3	3	2	9
70-79							1	4	5
80-89					1			1	2
Total	2	1	1	1	3	12	6	14	40
						32			

Type of Heart Disease.—Table II shows the distribution according to age and according to the etiologic type of heart disease. The heart was normal in only two cases. One patient had a congenitally hypoplastic aorta with cardiac failure; one had subacute bacterial endocarditis, probably engrafted on rheumatic valvulitis; one had fatal myocardial failure three weeks post partum; three had syphilitic aortitis with aortic regurgitation. The remaining 32 patients (80 per cent) had either hypertensive or arteriosclerotic heart disease; the two were usually, but not invariably, associated. In thirty-five of this series congestive heart failure was present before the appearance of the paroxysmal tachycardia

TABLE III
TABULATION OF THE VARIOUS ATRIAL RATES AND THE GRADE OF A-V BLOCK IN THE INDIVIDUAL CASES

CASE NO.	ATRIAL RATE	GRADE OF BLOCK	CASE NO.	ATRIAL RATE	GRADE OF BLOCK	CASE NO.	ATRIAL RATE	GRADE OF BLOCK	CASE NO.	ATRIAL RATE	GRADE OF BLOCK
1	174-179 187-190	1:1 4:3, 3:2 W	12	200	5:4, 4:3 W	22	207 222 255	1:1 3:2 W 2:1	31	162	6:5 W CSP 4:1, 6:1
2	184-192	2:1	13	125 N node 165	Complete						
3	272	6:4, 5:4, 4:3 W	14	182	8:7, 7:6 and less	23	196 Prostig. 182 Resp.	1:1 2:1	32	150-160	2:1, 3:2
4	158 187 190 194	2:1 2:1 2:1 2:1	15	193 187-190 102-105	Rare 1:1 3:2 and less W	24	156-176 171-179	2:1, 3:1 2:1, 3:2 W	33	156	2:1, 4:1 with vent. esc.
5	250-255	CSP 3:1, 4:1 2:1	16	162 Deep resp. 144-150 CSP	1:1 5:4, 2:1 W 2:1, 6:5 W	25	167 182	1:1, 12:11 W 4:3, 3:2, 2:1 W	34	150	3:2, 6:5 and less
6	164-187	6:5, 9:8, 23:22 W		Quinidine 143-158	3:1 with vent. esc.	26	196 260	2:1 2:1, 3:1	35	193-207	3:2, 2:1
7	273-286	2:1	17	158-164 214-240	1:1 1:1	27	214 200	1:1 2:1	36	171-193	3:2, 2:1, 3:1
8	182 200-203	1:1 4:3, 3:2 W		160-169	4:3, 11:10, and less W			CSP 3:1 with Resp. vent. esc.	37	207-214	2:1
9	125 143	1:1 8:7, 3:2 W	18	150-188	2:1, 9:8, 8:7 W	28	184-197	13:12, 9:8, 6:5, 2:1 W	38	158	6:5 and less
10	179	2:1	19	190	4:1 with vent. esc.	29	179-190	2:1	39	154	3:2
11	169 190-218	1:1 5:4, 3:2 W	20	167 179	1:1 5:4, 3:2 W	30	230-240	2:1	40	194-214	5:4, 8:7 and less

The presence of the Wenckebach type of block is indicated (W). The effects of earotid sinus pressure (CSP), of deep respiration, of prostigmine, and of quinidine are recorded in certain instances. Ventricular escape occurred with the higher grades of block. The grade of block is sometimes proportional to the atrial rate, e.g., Case 22; more often, factors other than the atrial rate seemed to determine the degree of A-V block.

with A-V block. In two instances failure was precipitated by the rapid heart action; in three cases there was no myocardial failure. Fifteen patients were studied at necropsy and in eight of these pulmonary embolism was found.

Medication.—Study of the records showed that the preceding medication played an important role both in the precipitation of the tachycardia and in the production of A-V block. Only seven patients had received no digitalis. Of the remaining thirty-three, twenty-three had an obvious overdosage of digitalis. The other ten had received what appeared to be reasonable doses, but they may have been too much for these particular patients. A history of previous digitalis administration may have been overlooked or not recorded. In these thirty-three cases, digitalis medication preceded, and may have precipitated, the tachycardia in twenty-five instances. In six cases digitalization caused A-V block in a pre-existing tachycardia; in the remaining two the block was definitely induced by prostigmine. Prostigmine was used in another case without effect.

In three cases the tachycardia with block appeared immediately after large diuresis due to mercurpurin. We interpret this phenomenon as a consequence of overdigitalization resulting from diuresis. Aminophylline administration preceded the tachycardia in ten cases, in seven of which it was given by vein. In one instance the block appeared immediately after the intravenous use of aminophylline. Coramine was given to three of the patients, but we cannot say that it contributed to the development of tachycardia, either with or without block. Quinidine was given to six patients, and may well have contributed to the impaired A-V conduction.

The grade of A-V block varied somewhat. The most common type was 2:1, which was recorded in twenty-one patients. Progressive increases (Wenckebach periods) occurred in twenty-two cases. There were 4:3 and 3:2 in eighteen electrocardiograms, with lower grades of 5:4 to 10:9 in fifteen, and still lesser grades in six. Nine patients, on the other hand, developed higher grades of block: 3:1 was recorded six times, 4:1 four times, and 6:1 once.

Increased conduction disturbances were produced by carotid sinus pressure in four electrocardiograms, whereas respiratory changes increased the block in two cases and change of position produced this in one instance. There were other electrocardiographic abnormalities of note. The intraventricular conduction time was increased during the paroxysm in eight cases.

The P-P cycle length showed alternation in nine instances; the cycle containing the ventricular complex was shorter than the following one in which A-V conduction was blocked. This was probably due to vagal reflex inhibition of the ectopic pacemaker, similar to that demonstrated by Ashman and Gouaux¹⁴ in complete A-V block.

TABLE IV

<i>Grades of Block</i>				
6:1	1	} 9 cases	4:3, 3:2	18 cases
4:1	4		5:4 to 10:9	15 cases
3:1	6		Less	6 cases
2:1	21 cases		Wenckebach type of block	22 cases
Carotid sinus pressure increased block			4 cases	
Respiratory change increased block			2 cases	
Postural change increased block			1 case	
Delayed I-V conduction during paroxysms			8 cases	
P-P cycle change with block			9 cases	
Pulmonary embolism and infarction			8 cases	(15 necropsies)
<i>Auricular Rate and Grade of Block</i>				
RATE	NO. OF CASES		GRADE OF BLOCK	
<150	3		rare block → 3:1	
150-199	26		rare block → 6:1	
200-249	9		5:4	
>250	5		5:4	
<i>Associated Atrial Mechanism Disturbances</i>				
	BEFORE A-V BLOCK		AFTER	INDIVIDUAL CASES TOTAL
Atrial paroxysmal tachycardia	11		6	12
Atrial premature beats	7		7	10
Atrial fibrillation	6		4	9
Atrial flutter	1		3	4
Shifting pacemaker	2		1	3
Delayed A-V conduction	1		2	2

TABLE V

MEDICATION
(AS CONTRIBUTING FACTOR TO TACHYCARDIA AND BLOCK)

DIGITALIS	CASES		CASES
None	7	} ↔ 33	6
Moderate doses	10		25
Overdosage	23		2
MERCUPURIN	3	PROSTIGMINE	2
QUINIDINE	6	CORAMINE	3
AMINOPHYLLINE	10 (7 i.v.)		
HEART FAILURE			
Absent			3
Induced by tachycardia			2
Present before tachycardia			35

Associated atrial mechanism disturbances were present in many cases before and after the time during which A-V block was recorded. Other attacks of uncomplicated paroxysmal atrial tachycardia antedated the block attack in eleven cases and postdated it in six cases in twelve patients. Atrial premature beats were recorded before the block attack seven times and after it seven times in ten patients. Atrial fibrillation was present in six instances preceding the paroxysmal tachycardia with block, and, subsequently, four times in nine patients. Flutter was

present one time before, and three times afterward, in four patients. Delayed A-V conduction had been present in two earlier electrocardiograms and occurred in one instance in the later electrocardiogram in two patients. A shifting pacemaker was recognized in two patients before the paroxysmal tachycardia with block attack, and once afterward.

DISCUSSION

It must be explicitly stated that we do not possess absolute criteria for sharp differentiation between atrial tachycardia and flutter. We have set down the criteria which have guided us, the most basic of which is the presence or absence of an isoelectric mechanism. Even this may not be valid, for a circus mechanism has been postulated for tachycardia.^{19, 20} We do not propose to discuss this possibility further at this time, for we have excluded from this series several instances in which paroxysmal tachycardia was closely associated with definite flutter or fibrillation, and are studying this association further. In our opinion, the cases illustrated conform to the criteria cited, although it is certainly desirable to obtain more absolute criteria for sharper differentiation.

In studies that are among the earliest of electrocardiographic-pharmacologic experiments, Lewis, White, and Meakins²¹ showed that the atrioventricular junctional tissue is most susceptible to influences which depress conduction. Lewis, Drury, and Hiesen²² found that among the influences that produced block were asphyxia, increased atrial rate, vagal stimulation, and strophanthin. Local increases in hydrogen-ion concentration have been found to have a similar effect. Our observation that A-V block occurs rather frequently in paroxysmal atrial tachycardia, particularly in hearts that are affected by myocardial disease, or which have been subjected to digitalis or quinidine medication, is merely clinical confirmation of these older experimental observations. Wilson and Wishart²³ comment on the rarity of block in paroxysmal tachycardia, as compared to its frequency in flutter, but refer to one instance of their own in which digitalis and added vagal tone did induce block. They also illustrate a case in which two paroxysms terminated with blocked atrial complexes.

Tachycardia of the type under discussion occurs commonly in normal hearts. However, only two hearts of the present series could be called normal (Cases 6 and 21). In Case 6 the patient had been given moderate doses of digitalis, and in Case 21 he had received an obvious overdosage. In other words, every patient included in this study had either myocardial disease, coronary or aortic disease conducive to myocardial anoxemia, or had received digitalis. In two instances the vagotonic effect of prostigmine was an added factor in producing A-V block. Most of the patients had disease of the myocardium and had received, in addition, digitalis, quinidine, or both. In our experience, such influences produce A-V block not uncommonly, although its appearance in normal hearts is distinctly rare.

The high incidence of A-V block among our records of paroxysmal tachycardia is probably due to the fact that most of the records were obtained from patients who had been hospitalized for cardiac disease. In fact, the majority of them had disease extensive enough to have led to congestive heart failure.

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THE NORMAL HUMAN VENTRICULAR GRADIENT

III. THE RELATION BETWEEN THE ANATOMIC AND ELECTRICAL AXES

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IN THE first paper of this series¹ we presented the results of our study of the directions of the QRS axis and QRS-T axis, with reference to their projection on the frontal plane of the body, and the relation between the axes as these were influenced by apparent rotation of the heart about anteroposterior, transverse, or longitudinal axes. We also examined certain normal influences which seemed to cause a change in the relation between the axes. In the second paper² we inquired into the manifest magnitudes of the QRS (A_{QRS}) and QRS-T (G) vectors, the projections of the spatial vectors, $S\hat{A}_{QRS}$ and $S\hat{G}$, upon the frontal plane, and into the factors which affected those magnitudes. We were able to demonstrate that the magnitude of the manifest QRS area (A_{QRS}) was chiefly influenced by physical causes, namely, changes in the position of the heart within the thoracic cage, whereas the manifest area, G , or the ventricular gradient, was increased or decreased not only by the same factors which changed the manifest magnitude of the QRS area, but also by physiologic conditions, such as changes in the heart rate and, perhaps, in the ventricular stroke volume. In order to make clear the reasons for the effect of changes in position, it was necessary to anticipate the material of the present paper. Although extended discussion was avoided, it was stated that we were mainly concerned with three axes, namely \hat{A}_{QRS} , \hat{G} , and a longitudinal anatomic axis around which the heart could rotate. This paper will describe these three axes, together with the anteroposterior and transverse axes of rotation, and will define, with the evidence, the spatial relations of the first three.

1. *Anatomic and Physiologic Considerations*.—The cardiac ventricles are located in the thoracic cavity and rest upon the diaphragm. In the average cardiac position, the atrioventricular valve openings are somewhat above and to the rear; the cardiac apex is somewhat below and near the anterior thoracic wall. As viewed from the front, the anterior surface of the ventricles is largely right ventricular wall, and a larger or smaller extent of left ventricular surface is visible to the left of the interventricular groove. If there is clockwise rotation of the heart about a long axis, less of the left ventricular surface is visible; if there is counterclockwise rotation, more of that surface is seen. In most hearts, the whole right border, from the root of the superior vena cava or aorta to the diaphragm, is formed by the right auricle. In other hearts, a

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small part of the right ventricular border is visible between the diaphragm and the right auricular border. Because of these differences it is likely that no method of ascertaining the long axis of the ventricles is quite accurate, and for convenience we have chosen the line drawn from the aortic-atrial angle to the ventricular apex as the longitudinal anatomic axis.

On excitation, the ventricles presumably are activated by impulses delivered by way of the bundle branches and their subdivisions. Since we are dealing with the axes as they are recorded or calculated, rival theories of the mode and sequence of ventricular excitation do not concern us. The facts of animal experimentation, of which the latest and probably the most useful study is that of A. Sidney Harris,³ demonstrate that the epicardial surface of the anterior, apical, right and, in part, anterior left ventricular walls is the first to become fully activated in the monkey. The left ventricular base and the pulmonary conus are latest. In the dog and cat the time relations are similar, although not identical. This may readily be interpreted as meaning that the *instantaneous* electrical axis of QRS initially points forward and downward. But this direction is not long maintained. The instantaneous axis rapidly rotates, to right or left, and comes to point more or less backward, and finally even upward, in most hearts. The relatively backward direction, being longer maintained, causes the *mean* axis of the QRS to point in a backward direction relative to the anatomic axis. A paper by Gardberg and Ashman⁴ considers in detail the electrocardiographic consequences of this upon the instantaneous electrical axes which compose the QRS complex.

After inscription of the QRS complex, the RS-T segment and T wave are written. The repolarization of the muscle has begun in the regions earliest to enter into activity before the activation of the whole muscle mass is complete. Hence, any displacement of the S-T segment, not due to disease, is considered to be a part of the T complex. Repolarization of the ventricles, as explained in our first paper, occurs in general in a direction which differs from the order or sequence of depolarization. In other words, the orders of accession and regression are not the same.⁵ This is the reason for the existence of the ventricular gradient, and, as a matter of fact, the orders of accession and of regression are nearly opposite, under usual, normal conditions. It is most convenient to assume that the subepicardial muscle fibers, in general, recover more promptly than the subendocardial fibers, and it may eventually be found that the major effects in the production of the gradient are within the left ventricular walls, including the septum.

Since the mitral and aortic valve openings cannot participate in this, the unbalanced electrical forces are directed approximately, although almost certainly not precisely, opposite the valve openings. If all the left ventricular walls shared equally in producing the effect, and the

right ventricle not at all, the axis of QRS-T (\bar{G}) would then point from the center of the combined valve openings on the left, out through the wall opposite the openings. To the extent that the position of the heart shifts during systole, will the direction of the electrical forces then produced experience a change in direction. It appears possible that the leftward shift of \bar{G} , which was stated to occur under some, although not under all, conditions of cardiac acceleration, is due to this.

Our present problem is to ascertain the *apparent* directions of the mean spatial QRS ($S\hat{A}_{QRS}$) and QRS-T ($S\bar{G}$) axes, relative to each other, and relative to the anatomic axis.

2. *Materials Used.*—These were the same as those described in the second paper of this series. In addition, orthodiagrams or roentgenograms were obtained on eighteen subjects, and measurements were made of the anteroposterior chest diameter at the level of the fourth intercostal space at the sternum, together with measurements of the transverse thoracic diameter at the level of the cardiac apex. With the permission of the author and the publishers, we have also made extensive use of the excellent roentgenograms and electrocardiograms in Master's book.⁶

3. *Estimation of the Size of the Angle Between the Mean Spatial QRS ($S\hat{A}_{QRS}$) and QRS-T ($S\bar{G}$) Axes.*—In the first paper, it was shown that when the ventricles are rotated in a clockwise direction around the longitudinal axis of rotation, \hat{A}_{QRS} lies to the right of \bar{G} , and it was shown that counterclockwise rotation causes \hat{A}_{QRS} to lie to the left of \bar{G} . It was pointed out that this can only mean that the directions of the two axes are different and that the spatial axis, $S\hat{A}_{QRS}$, points backward relative to the spatial axis, $S\bar{G}$. But it is apparent that the angle between $S\hat{A}_{QRS}$ and $S\bar{G}$, the ventricular gradient, is not correctly reflected in the projection of these axes on the frontal plane. Reference to Fig. 1 will make it easy to see that when the QRS axis is directly behind the QRS-T, their directions relative to the frontal plane will be the same. On the other hand, if the longitudinal axis of rotation (II) were in the frontal plane, and if the heart were rotated sufficiently about the II axis, either clockwise or counterclockwise, both axes would come to lie in a plane parallel to the frontal plane, and the angle between them would be the true angle. At the same time the manifest areas would be at their maximum.

a. In order, therefore, to attempt to ascertain the true size of the angle, we may select those few cases which show nearly maximum net QRS areas, and nearly maximum QRS-T areas for the heart rate. The true angle should be no smaller than the recorded angle, although it will probably be larger, since the required rotation may not normally occur, and the axis of rotation will not often be in the frontal plane. Furthermore, since we have found that normal, counterclockwise rotated hearts do not show maximal QRS and QRS-T areas in our series of cases, we may confine our search to hearts with clockwise rotation. We must not forget, also, that unavoidable error in measurement may give us

angles which are several degrees too large or too small. The result of this method shows that the four largest angles, directly recorded, are 19, 20, 22, and 23 degrees, respectively. Allowing for error, the angle between the QRS and QRS-T axes is, therefore, greater than the average of those figures, or 21 degrees. The larger angles seen in Fig. 2 of the first paper can be ascribed to foreshortening of the angle as projected upon the frontal plane, and possibly to change in position of the heart during systole.

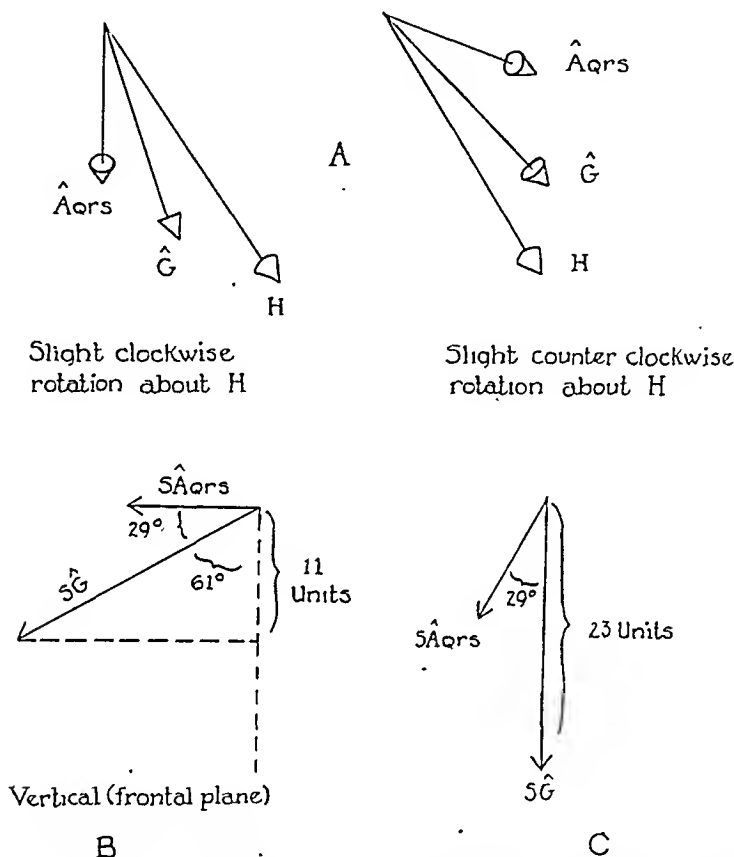


Fig. 1.—A, Showing relationship of axes as projected on the frontal plane, with clockwise rotation about H, on left, and counterclockwise rotation about H, on right. H points downward, forward, and to subject's left.
 B, The spatial axes as seen in a right lateral view when the axes lie in a sagittal plane. The vertical dotted line marks the intersection of frontal and sagittal planes.
 C, The spatial electrical axes after rotation of the heart so that $\hat{S}\hat{G}$ marks the intersection of frontal and sagittal planes. Described in text.

It should be said that the normal absence of extreme rotation, and absence of angles larger than 23 degrees when the areas are nearly maximum, are facts worth recording.

b. A trial and error method of ascertaining the size of the spatial angle between $\hat{S}\hat{A}_{QRS}$ and $\hat{S}\hat{G}$ was the one we first employed. Using a model showing the longitudinal axis of rotation, H, and the two electrical axes, the several axes can be drawn on the roentgenogram and the sizes of the angles chosen to give the best fit of all three axes (Fig. 1). Proceeding in this fashion, we arrived at an angle between the two electrical axes, $\hat{S}\hat{A}_{QRS}$ and $\hat{S}\hat{G}$, of about 31 degrees, and an angle of about 59 degrees between H and $\hat{S}\hat{G}$.

c. The third method will be clearer if we refer to the axes as shown in Fig. 1, *B* and *C*. These diagrams show the $S\bar{A}_{QRS}$ and $S\bar{G}$ axes as they would appear if seen from the right side of the body. In *B* of the figure, $S\bar{A}_{QRS}$ points directly backward, so that its net area, as projected on the frontal plane, is zero. From the slope of the highest G values at different magnitudes of A_{QRS} , in Fig. 2 of our previous paper, it may be inferred that when A_{QRS} is zero, the maximum G value is about 11 units (44 microvolt-seconds). We may now imagine that the axes are rotated about a transverse axis to the position shown in Fig. 1 *C*. $S\bar{G}$ is now parallel to the frontal plane, and its projected value, G , is now at its maximum. In the previous paper, we found this maximum value to be 23 units. These data, 11 units and 23 units, enable us to calculate the angular rotation of $S\bar{G}$ as it moves from the position shown in *B* of the figure to the position in *C*. G , the projected value, will grow as the cosine of the angle between it and the frontal plane. The ratio, 11:23, is 0.478. This corresponds to an angle of 61 degrees and 27 minutes, which, in round numbers, we may call 61 degrees. As is evident from *B* of the figure, 90 degrees, the angle between $S\bar{A}_{QRS}$ and the frontal plane, minus 61 degrees, or 29 degrees, is, therefore, the angle between $S\bar{A}_{QRS}$ and $S\bar{G}$, according to this calculation.

d. The fourth method of calculating the spatial angle between $S\bar{A}_{QRS}$ and $S\bar{G}$ need not be described in detail. It is obvious that when the heart is not rotated on its longitudinal axis, there will be a simple trigonometric relationship between the area, A_{QRS} , and the area, G , as the heart is rotated, about its transverse axis. We found twenty-six hearts with A_{QRS} values of 3.0 units (12 microvolt-seconds) or less, including negative values. Such areas preclude much rotation on II. The average value was 1.0 unit, and the average value of G was 8.4. Another group of twenty-seven nonrotated hearts had A_{QRS} magnitudes of over 3.0 units; the average was 7.0 units, and the average value of G was 13.9. In both groups, the values were those after adjustment to a heart rate of 80.⁵ If the magnitude, SA_{QRS} , is between 10 and 11 units (see below) it may be calculated that the spatial angle between $S\bar{A}_{QRS}$ and $S\bar{G}$ is 29 degrees. This agrees with the third method of calculation. Although there are valid mathematical objections to averaging the values used, this method should give a fairly good approximation.

In recapitulation of the four methods of calculating the angle between the two vectors, the first shows that the angle is somewhat greater than 21 degrees; the second, as first employed, indicated about 31 degrees; and the two calculations agree on nearly 29 degrees. We will be sufficiently correct, therefore, if we take 30 degrees as the true angle in the typical normal adult heart, with the subject in the supine position.

Unless we put in an emphatic comment at this point, the third analysis given (paragraph c) may be interpreted as meaning that in actuality the heart may rotate 61 degrees about a transverse axis when different

persons are compared. The calculation does not mean this. When A_{QRS} is zero, the heart cannot be in a position of rotation on its long axis. On the other hand, the maximum G values will usually be obtained in rotated hearts. If we assume that the same heart could show the required changes, it could rotate 30 degrees on a transverse axis and 30 degrees on H to change from the position of minimum manifest mean QRS area to that of maximum manifest mean QRS-T area. Such changes, when different subjects are considered, are certainly not extreme.

The Magnitude of the Mean Spatial QRS Vector.—We may now, in passing, attempt a rough, indirect calculation of the true magnitude of SA_{QRS} . Again referring to Fig. 2 of the previous paper,¹ we find that the average value of A_{QRS} , when G was 23 units, was about 9.5 units. After allowing for the fact that most of these hearts were somewhat rotated, that A_{QRS} , although large, could not have been quite at its maximum magnitude (since no heart in a normal chest can be strongly enough rotated to bring all three axes into the frontal plane), we may guess, trigonometrically, that A_{QRS} , the projection of SA_{QRS} , has about 85 or 90 per cent of the average magnitude of the latter when G is 23 units, and that the average of SA_{QRS} is, therefore, about 10.5 or 11 units, although it may possibly be somewhat larger. Since the persons in question were men, this may be regarded as the approximate average SA_{QRS} in that group. It is noteworthy that only eight A_{QRS} values in 270 subjects exceeded the value of 10.5 units, and that seven values lay in the range 10.4 plus-minus 0.1 units. No doubt, with respect to the values both of SG and SA_{QRS} , there is some individual variation. A few of our highest A_{QRS} values may, of course, be abnormal, particularly the four cases at 11.9 to 12.6 units, assuming their size was not overestimated. When a patient is found to have a large, carefully measured A_{QRS} (we may call 11 units the upper limit of the normal), it is obvious that the case should be analyzed to decide whether the large value is due to the position and rotation of the heart, or to changes produced by disease. This, of course, is also true of very small A_{QRS} values. Because of the narrowness of the QRS complex in young children, there can be no doubt that their average SA_{QRS} magnitude is considerably smaller than that of adults.

Our data may, of course, be subjected to further analysis of a mathematical type. For example, when the A_{QRS} values are negative, and the axis lies in the neighborhood of minus 110 degrees, the manifest mean area of QRS-T should be near the minimum, on the average. This agrees with the observed facts of our few such cases. The maximum values should, in general, be observed in hearts rotated rather strongly in a clockwise fashion which are not vertical, and this again is distinctly in accordance with the observed facts. These observations afford further evidence that the two axes are separated by an angle of fair magnitude,

and that rotations of various types and degrees are reflected with consistent faithfulness by the electrocardiogram. This statistical analysis, however, gives us no direct information regarding the angles between the electrical axes and the longitudinal axis of rotation, although this might be inferred, nor does it tell us the extent to which individual hearts may deviate from the averages. Many hints suggest that the latter divergences are not great. We will now proceed to a comparison of the electrocardiographic with the anatomic evidence. This should give us further information along the lines we have considered.

4. *The Size of the Angles Between the Several Axes, Estimated From a Comparison of the Electrocardiogram and the Cardiac Silhouette.*—As a preliminary to this study, by use of a model of the electrical and anatomic axes, we compared the directions of \hat{A}_{QRS} and \hat{G} , as shown by the electrocardiogram and the anatomic axis as shown by the roentgenogram. With the permission of the author and the publishers, we have drawn the silhouettes and thoracic outlines shown in our Figs. 2, 3, 4, and 5 from A. M. Master's valuable and instructive book,* so that these are available to the reader who may be interested in checking our observations against a reliable series of roentgenograms and electrocardiograms. To this series, we have added eighteen cases of our own. We may note here that our analysis fully vindicates Master in his insistence upon the importance of positional changes of the heart.

In our study of Master's figures, after a good bit of trial and error, we finally devised a model which had a 90 degree angle between the longitudinal anatomic axis of the heart and the mean QRS axis, and a 59 degree or 60 degree angle between the anatomic axis, H, and the ventricular gradient, the three being in the same plane (Fig. 1 A). The model was attached, by the lower end of its H axis, to a rubber ball, so that it could be rotated in front of a chart. The α angles were marked on the chart as radiating lines, and concentric circles were drawn around the center of radiation so that the net manifest mean area of the QRS complex (A_{QRS} values) could be represented. A source of light, nearly 30 feet distant and properly placed, projected the shadow of the model upon the chart. The model was then adjusted so that H on the model coincided with the direction of H shown by the cardiac silhouette. Keeping H fixed, further adjustments and rotations were made until the direction and the magnitude of \hat{A}_{QRS} were also correct for the heart being studied. The direction of \hat{G} was then read from the chart, and this direction is called the "calculated" \hat{G} (Tables I and II), which is then compared with the actual direction of \hat{G} as it was ascertained from the electrocardiogram. If, in the whole series of cases examined, the "calculated" and actual directions of \hat{G} are in good agreement, it may then be assumed that the angle between $S\hat{A}_{QRS}$ and $S\hat{G}$ chosen for the model is nearly the same as the true spatial angle. At the same time, the tables show the range of variation in axis directions in normal subjects. As

will be shown, if the electrocardiogram indicated clockwise or counterclockwise rotation, then in nearly all instances it was necessary to rotate the model in the corresponding direction to obtain a good agreement between the axes. In most instances, when the electrocardiogram showed that the apex should be tilted forward or backward, it was found that this movement resulted in better agreement between the calculated and observed relations. It will be seen that, since there were five

TABLE I

SUBJECT NO.	AGE AND SEX	AREA Λ_{QRS}	ROTATION *	H (DEGREES)	$\hat{\Lambda}_{QRS}$ (DEGREES)	\hat{G} (DEGREES)	CALCULATED \hat{G} (DEGREES)	DISCREPANCY, TO RIGHT OR LEFT OF CALCULATED (DEGREES)
4	10 mo. F	3.70	c5	+26	+74	+66	+56	10 R
5	5 F	5.20	c4	+39	+88	+63	+61	2 R
6	7 M	7.65	c4	+42	+97	+76	+77	1 L
7	12 M	7.60	c3	+48	+88	+69	+72	3 L
8	20 F	4.10	c1	+38	+68	+46	+51	5 L
9	30 M	5.75	cc3	+35	- 5	+15	+16	1 L
10	60 M	4.65	cc3	+35	- 5	+16	+19	3 L
11	75 F	7.30	cc5	+36	-34	- 8	- 2	6 L
12	81 M	6.70	cc5	+33	-28	- 9	+ 3	12 L
13 A	21 M	6.90	c3	+32	+42	+28	+38	10 L
13 B	21 M	8.20	c3	+43	+82	+67	+68	1 L
14 A	44 F	5.60	c2	+50	+77	+74	+65	9 R
15 A	73 M	4.30	cc3	+42	+20	+44	+32	12 R
15 B	73 M	3.70	cc2	+44	+54	+64	+48	16 R
16 A	12 M	8.35	c2	+30	+52	+42	+46	4 L
16 B	12 M	6.50	c3	+44	+83	+64	+66	2 L
17 A	12 F	2.60	c1	+34	+74	+39	+42	3 L
17 B	12 F	2.60	c1	+33	+74	+19	+42	23 L
18 A	27 F	7.75	cc3	+38	+18	+12	+25	13 L
20 A	29 M	2.00	cc1	+33	+25	+38	+29	9 R
21	45 M	6.30	c2-3	+43	+77	+69	+63	6 R
23 B	35 M	6.00	c3	+56	+92	+68	+73	5 L
24	21 M	7.40	c3	+54	+95	+81	+73	8 R
22†	15 M	4.50	cc2	+56	+50	+56	+54	2 R
25	26 F	8.10	c3	+46	+68	+42	+58	16 L
26 B	49 F	3.30	cc4	+26	-41	+ 1	+ 2	1 L
27	21 M	4.70	cc4	+30	-10	+11	+12	1 L
28 A	25 F	8.70	None†	+25	+30	+24	+28	4 L
29 A	33 F	5.40	cc1	+26	+13	+22	+20	2 R
29 B	33 F	5.20	None	+35	+32	+32	+33	1 L
31	52 M	9.20	cc4	+35	-24	+ 5	- 5	10 R
36	56 F	6.20	cc2	+38	+10	+20	+22	2 L
37	29 F	9.00	cc3	+46	+29	+31	+36	5 L
42	39 M	6.10	c1	+45	+59	+54	+51	3 R
44	27 F	6.80	c3	+47	+87	+64	+65	1 L
63 A	34 M	7.20	c1	+45	+65	+61	+58	3 R
73	13 M	8.00	c5	+47	+120	+81	+80	1 R
78	20 F	4.30	cc4-5	+60	+23	+50	+46	4 R
84 C	22 M	7.00	c3	+44	+60	+43	+53	10 L
97 B	16 M	4.50	c2	+44	+89	+56	+60	4 L

*c = clockwise rotation on long axis as shown by electrocardiogram. cc = counterclockwise rotation. The figures 1 to 5 represent the electrocardiographic picture of very slight to doubtful rotation, 1; slight, 2; definite, 3; marked, 4; extreme, 5.

†First edition of Master's book.

‡Varies with respiration.

The fact that there are more leftward than rightward deviations of G is probably due to the fact that the electrocardiogram was usually taken with the subject semi-recumbent, and the roentgenogram with the subject in a different position.

variables (the position of the three axes and the direction of rotation both about II and also about the heart's transverse axis), a good agreement, in the total series of cases, between the electrocardiogram measurements and the model cannot be due to chance. Table I gives a summary of the measurements.

We may now consider the figures from Master's book,⁶ indicating in parenthesis which of our figures correspond. Although the agreement with the model appears to be good, we omit Master's 20-day-old infant, and take his figure 4, from a normal infant, 10 months old. Here A_{QRS} is rather small, although individual deflections are large, and the deep Q_s and S_1 indicate strong clockwise rotation about II. As we measure them, \hat{A}_{QRS} is plus 74 degrees, \hat{G} is plus 66 degrees, and II is rather transverse, namely, plus 26 degrees. The heart rate is about 123 (average of Leads I and III). When the model was placed so that II agreed with the roentgenogram and \hat{A}_{QRS} agreed with the electrocardiogram, \hat{G} was about 56 degrees, differing by 10 degrees from the expected figure. It has been assumed that, in the infant, the net area of the mean QRS vector is normally smaller than in the adult because of the narrowness of the QRS complex, and correction was made accordingly. In any event, we regard the agreement as good.

It may be noted at this point that the electrocardiographic measurements, the estimation of the direction of the anatomic axis from the cardiac silhouette, and the estimate of the direction of \hat{G} , by use of the model, are all obviously subject to error. The electrocardiogram and roentgenogram were taken with the subject in slightly different positions in most cases. In view of these possibilities of error, the agreements shown appear to us to be very good.

In figure 5 (Fig. 2 *A*) we read \hat{A}_{QRS} , plus 88 degrees; \hat{G} , plus 63 degrees; II, plus 39 degrees. The magnitude, A_{QRS} , is nearly average. Here the model shows a \hat{G} of plus 61 degrees. The expected and observed angles agree within 2 degrees, certainly far less than the errors inherent in the method. Master's figures 6 and 7 (Fig. 2, *B* and *C*) also show excellent agreement. Figure 8 (Fig. 2 *D*) shows a difference of 5 degrees, but A_{QRS} is small, increasing the probable error of the method. The electrocardiogram in this case shows a Q_1 and a larger S_1 , with a trace of S_2 . From the criteria in Gavrilberg and Ashman's paper, we judge this to be an example of slight clockwise rotation about II, and this is confirmed by the fact that the peak of R_1 is earlier than the peak of R_2 . As inspection of the model will show, when the magnitude, A_{QRS} , is small, a slight rotation about II will produce a considerable angle between II and \hat{A}_{QRS} . Figure 9 (Fig. 3 *A*) shows a considerable degree of counterclockwise rotation about II, and, as expected, \hat{G} lies to the right of \hat{A}_{QRS} . The agreement between the electrocardiogram and the model is excellent. Likewise, figures 10 (Fig. 3 *B*), 11 (Fig. 3 *C*), and 12, all counterclockwise by Wilson and Johnston's 'vectorcardiogram' and by

Gardberg and Ashman's and other criteria, are in accordance with expectations, although figure 11 (Fig. 3 C) is from a 75-year-old woman, and figure 10 from an 81-year-old man. The latter shows a tolerable discrepancy of some 12 degrees. In Master's figure 13 (Fig. 3 D) there is some uncertainty regarding the anatomic axis. If it is taken as about

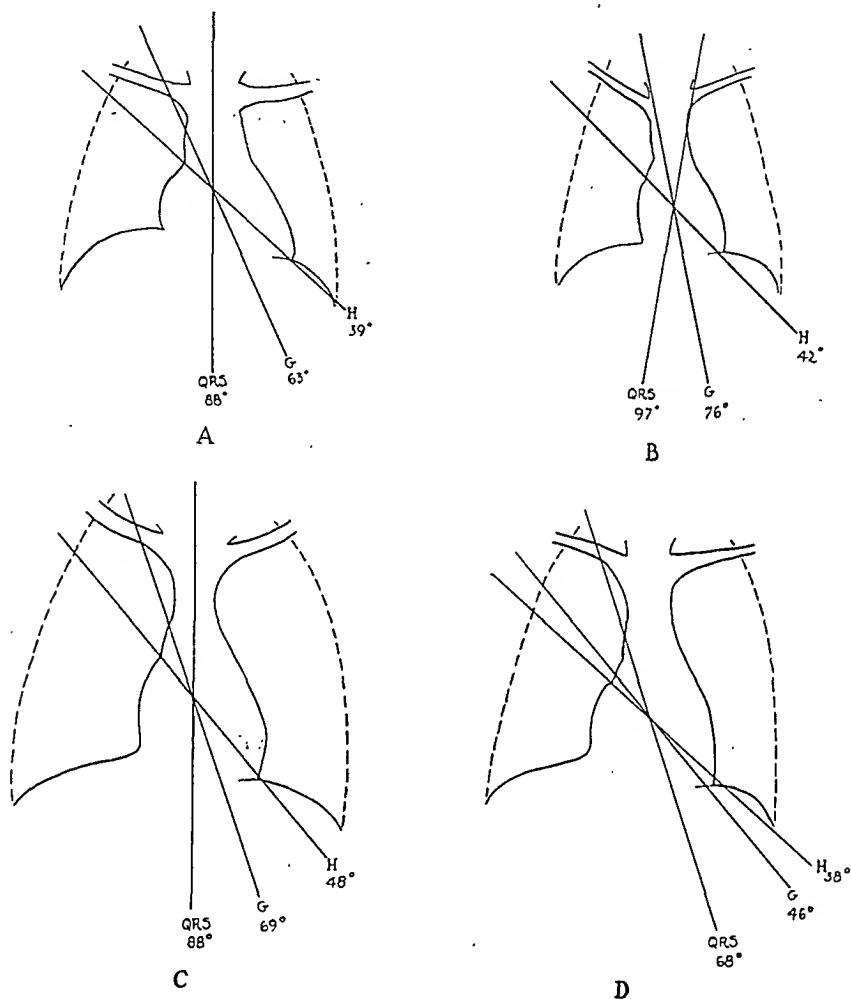


Fig. 2.—A, B, C, and D are, respectively, from figures 5, 6, 7, and 8 of Master's book.

plus 33 degrees, then the discrepancy between the actual and the expected \bar{G} is about 10 degrees. Figure 13 (Fig. 4 A), from the same subject on deep inspiration, gives a practically perfect fit. Figures 14, A, B, and C, from one subject, show discrepancies of not over 9 degrees or 10 degrees; in other words, the agreement is good. Figure 15 A is from a 73-year-old man whose electrocardiogram shows moderate counterclockwise rotation. H is about plus 42 degrees; \hat{A}_{QRS} , plus 20 degrees; and \bar{G} is plus 44 degrees. The magnitude, A_{QRS} , is a little below average. Here the discrepancy is about 12 degrees. Figure 15 B is from the same subject during deep inspiration. The electrocardiogram picture of counterclockwise rotation is less pronounced. The anatomic axis appears to be about the same as before. But \hat{A}_{QRS} has rotated to plus 54

degrees and \bar{G} to plus 64 degrees. The magnitude, Δ_{QRS} , has decreased. To obtain a fit between the model and $\bar{\Delta}_{QRS}$ we must rotate the model slightly clockwise, opposite to the direction shown by the electrocardiogram. And \bar{G} by the model is about plus 48 degrees, against the electrocardiogram measurement of plus 64 degrees. Only larger experience will show whether these two discrepancies are within the normal limits.

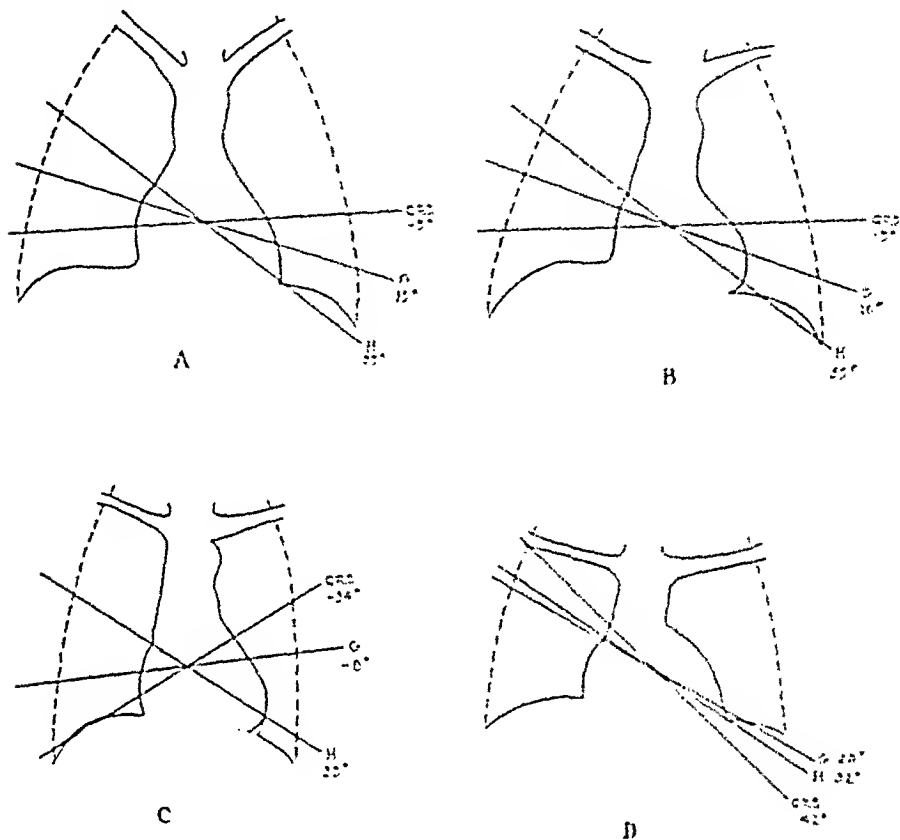


Fig. 3.—A, B, C, and D are, respectively, from figures 9, 10, 11, and 13 A of Master's book.

Theoretically, both changes could result from an old anterior lesion, but the rightward deviation of G may indicate emphysema, instead. The lesser counterclockwise rotation on inspiration could rotate an anterior lesion so that it would affect the limb leads. It is interesting to note that, in this case, deep respiration was required to reveal the possible abnormality.

Master's figure 16 A (Fig. 4 B), in which the electrocardiogram is interpreted as showing slight clockwise rotation, and 16 B (Fig. 4 C) (deep inspiration) show no discrepancies. Figures 17 A and B, from the same subject, show very slight clockwise rotation, as we interpret them. The small Δ_{QRS} , as noted above, tends to exaggerate errors. The anatomic axis in figure 17 A is plus 34 degrees; Δ_{QRS} , plus 74 degrees; and \bar{G} , plus 39 degrees. The wide angle between Δ_{QRS} and \bar{G} is mainly due

to the effect of "foreshortening," and G is very close to its expected position. In figure 17 B , in the sitting position, the H and \hat{A}_{QRS} have changed little. G , however, has shifted to plus 19 degrees from plus 39 degrees. This phenomenon is not abnormal, however, as our previous papers stated. On changing the position from recumbent to sitting, and particularly to standing, the gradient usually shifts to the left, and evidently it may shift to the left of H , while A_{QRS} remains on the right, as

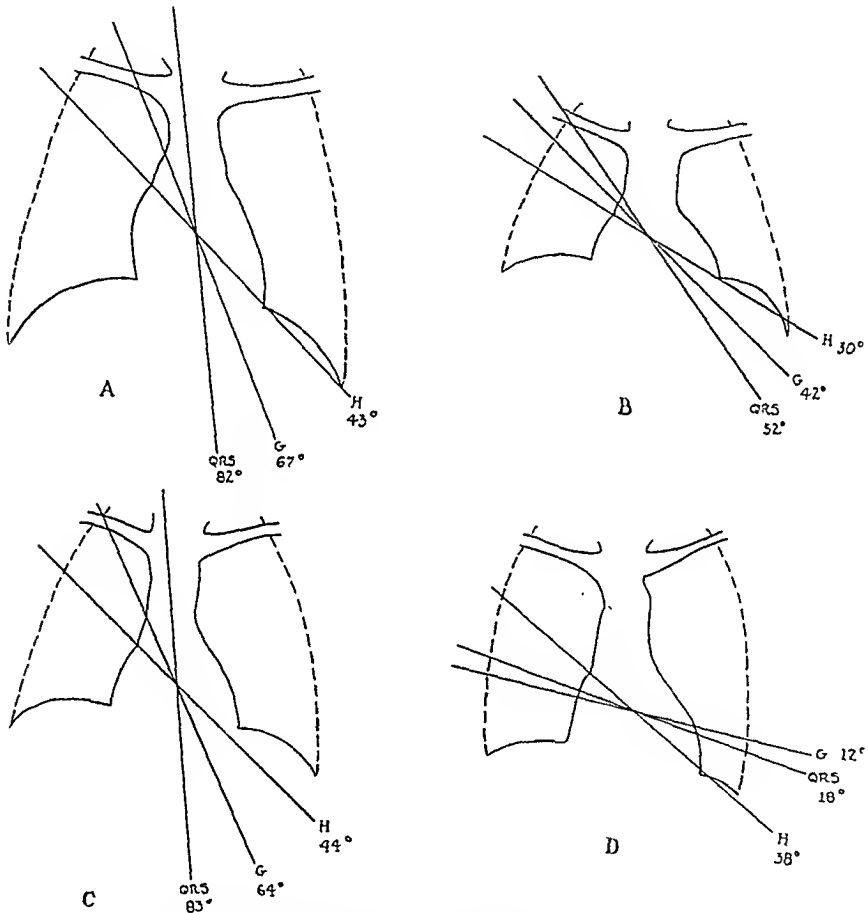


Fig. 4.— A , B , C , and D are, respectively, from figures 13 B , 16 A , 16 B , and 18 A of Master's book.

in this case. The three axes cannot now lie in the same plane. Tentatively we ascribe this effect of posture, in part, at least, to a greater change in the systolic position of the heart than occurs in the recumbent position. Figure 18 A (Fig. 4 D) shows a definite counterclockwise rotation, and the gradient is about 13 degrees farther to the left than expected. But here both a sitting position and the rapid heart may combine to produce this effect, which is normal under the circumstances. We have not attempted to measure figures 18 B and C and 20 B and C , which were taken in the lateral recumbent positions; and we also omit the abnormal records of fixed mediastinum shown in figures 19 A , B ,

and C . Figure 20 A (Fig. 5 A) shows a discrepancy of about 9 degrees. H is plus 33 degrees; \bar{A}_{QRS} , plus 25 degrees; and \bar{G} , plus 38 degrees. \bar{G} should lie at about plus 29 degrees. There is a slight counterclockwise rotation, since S_2 is larger than S_1 , a small Q_1 is present, there is no Q_2 , and the peak of R_2 is earlier than the apex of R_1 . The net area, A_{QRS} , is exceptionally small. Figure 21 (Fig. 5 B) shows good agreement.

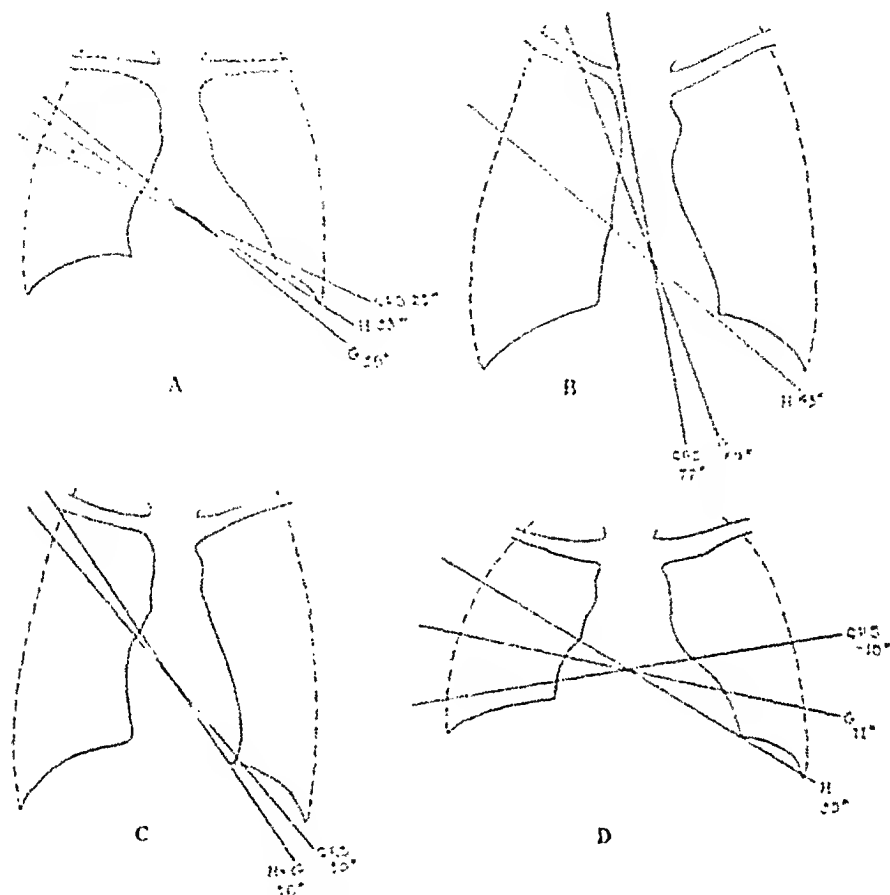


Fig. 5.— A , B , and D are, respectively, from figure 20 A , 21, and 27 of Master's book. C is from figure 22 of the first edition of his book.

Figure 22 illustrates the derivation of the electrical axis. Figures 23 B and 24 are in good accord with expectations. Our Fig. 5 C is figure 22 of the first edition of Master's book; it was a vertical heart, with slight to moderate counterclockwise rotation, in a 15-year-old boy, and the calculated G lies within 2 degrees of the actual one. In figure 25, the minute rate of 115, and possibly a sitting position, will account for the deviation of 17 degrees to the left of the expected \bar{G} position. Here, with very little clockwise rotation, G and H are close together. Figure 26 B is particularly noteworthy. This obese subject, whose anatomic axis is plus 26 degrees, has an \bar{A}_{QRS} at minus 41 degrees and a \bar{G} at plus 1 degree. Yet the agreement is excellent, the calculated \bar{G} being plus 2

degrees. Figure 27 (Fig. 5 *D*) agrees with the model: H, plus 30 degrees; G, plus 11 degrees; \hat{A}_{QRS} , minus 10 degrees: There is, of course, counterclockwise rotation in the electrocardiogram. Figure 28 *A* shows all the axes lying within a few degrees of each other, the rotation apparently varying very slightly from clockwise to counterclockwise with respiration. Figures 29, *A*, *B*, and *C* are from a patient who was six months pregnant. The electrocardiogram shows slight counterclockwise rotation about H, which practically disappears on deep inspiration. Agreement with the model is good. It is particularly interesting that in figure 29 *B*, as in 28 *A*, when there is little rotation, the axes all lie within a few degrees of each other, as they should. It is also noteworthy that figure 31, from a case of arterial hypertension, shows almost the normal relations of the axes: H, plus 35 degrees; G, plus 5 degrees; and \hat{A}_{QRS} , minus 24 degrees. Figure 32, a more advanced case, with angina pectoris, shows: H, plus 25 degrees; G, plus 66 degrees; \hat{A}_{QRS} , 0 degrees. The model will not fit this combination of axes, but it should be noted here that when the QRS complex becomes enlarged, or abnormal, the relations we describe can no longer hold. It may also be noted that some of the less advanced cases of valvular disease fit the model as well as do normal subjects.

In recapitulation, not one of the series of normal subjects from Master's book displayed any discrepancy which was not well within the

TABLE II

SUBJECT NO.	SEX	HEART RATE	AREA A_{QRS}	ROTATION (ECG) *	H (DEGREES)	\hat{A}_{QRS} (DEGREES)	ACTUAL G (DEGREES)	CALCULATED G (DEGREES)	DISCREPANCY, TO RIGHT OR LEFT OF CALCULATED (DEGREES)
1	M	60	4.60	c3	+31	+71	+50	+50	0
2	M	75	4.25	c4	+34	+90	+61	+53	9 R
3	M	70	1.35	cc1	+36	+30	+30	+33	3 L
4	F	84	6.00	c3	+41	+86	+55	+64	9 L
5	F	72	5.30	c2	+49	+68	+46	+57	11 L
6	M	97	6.10	c1	+34	+61	+44	+50	6 L
7	F	118	6.20	c3	+51	+90	+74	+71	3 R
8	M	114	-1.00	c1	+50	-77	+56	+49?	7 R
9	F	120	4.10	c2	+44	+82	+46	+60	14 L
10	F	63	9.05	c3	+30	+74	+58	+61	3 L
11	M	75	5.10	cc1	+33	+32	+25	+32	7 L
12	M	110	-3.50	c1?	+52	-107	+51	+40?	11 R
13	M	86	8.55	c3	+30	+58	+40	+49	9 L
14	M	120	8.30	c4	+42	+114	+86	+85	1 R
15	M	90	0.85	0	+36	+43	+20	+37	17 L
16	M	78	6.60	c3	+42	+69	+49	+57	8 L
17	M	90	4.70	c3	+42	+93	+70	+65	5 R
18	M	100	21.00†		+44	+77	+67		

*For significance of the symbols, see Table I.

†This subject had a Wolfe-Parkinson-White syndrome, with high, wide, R waves. Therefore, the QRS axis is not comparable with the normal complexes. The gradient indicates a clockwise rotation, which is what would be expected from his hyposthenic build.

Cardiac silhouette and electrocardiogram were obtained in the same position for all subjects.

limits of normal variation, as previously reported. In one case (Figure 15), indeed, deviations from the normal were noted, but the patient was well advanced in years.

In Figs. 6 to 9, we show the cardiac silhouettes and axes of sixteen persons from our own series of normal subjects. One case, which we have omitted, to save journal space devoted to figures, is an average, typical case in which there is excellent agreement between expectations

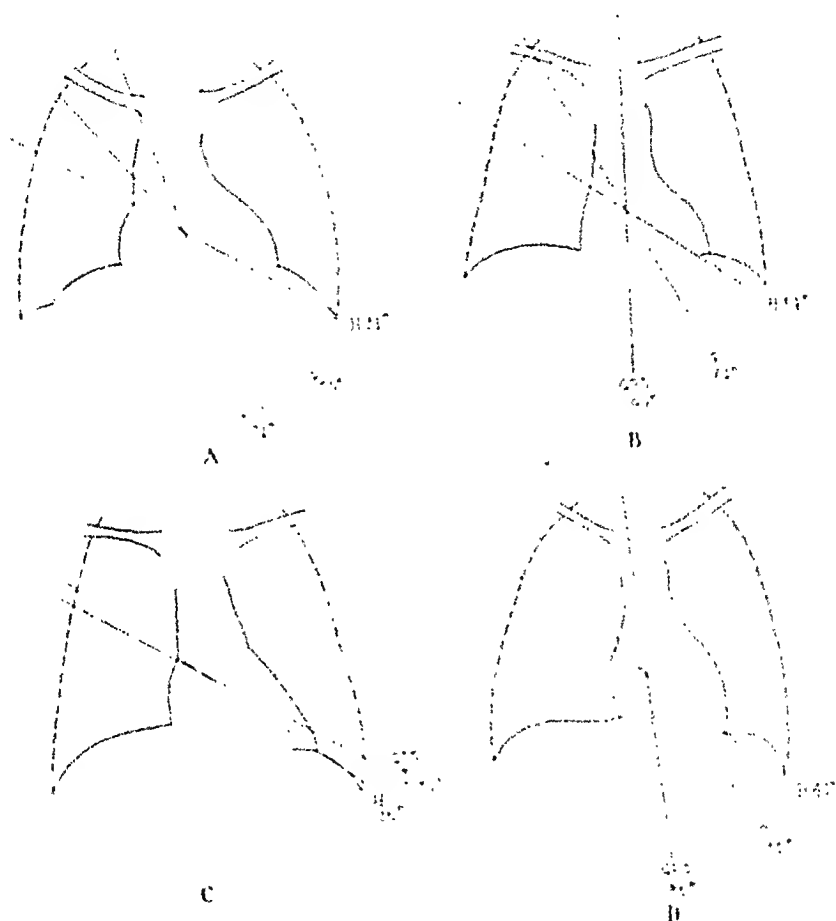


FIG. 6.—A, B, C, and D are, respectively, from roentgenograms of our Subjects 1, 2, 3, and 4 of Table II.

and predictions. The other was a case of the Wolfe-Parkinson-White syndrome, with greatly enlarged QRS complexes. In this case the heart was vertical and \bar{G} was at plus 65 degrees. The orthodiagrams or roentgenograms and the electrocardiograms were taken with the subject in the sitting or standing position, as stated in the figure captions. Since the subjects were seated or standing, it is to be expected, as reported in our first paper, that the gradients will often lie farther to the left than in recumbent subjects. In order to save space, the results of this study are given in Table II.

These data require comment. It will be observed that, in six cases, the agreement between \hat{G} , as ascertained from the electrocardiogram, and as estimated by means of the model, is within 5 degrees, and this is true of our first omitted case. Of the remaining eleven cases, eight

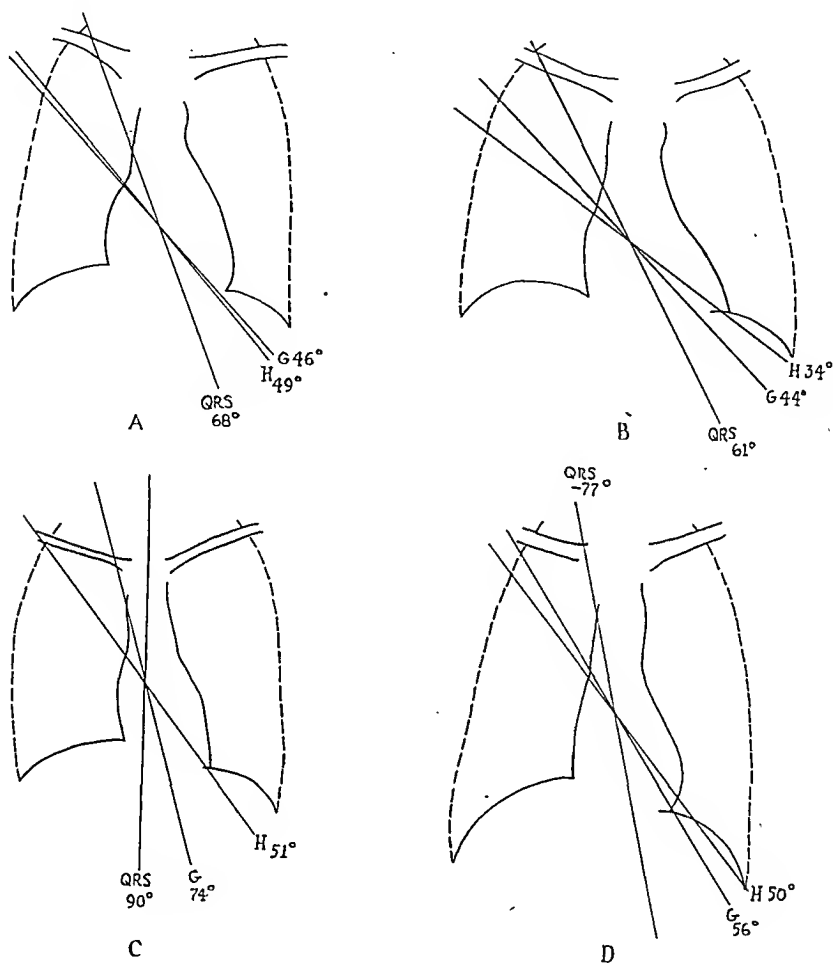


Fig. 7.—A, B, C, and D are from roentgenograms of our Subjects 5, 6, 7, and 8, respectively, of Table II.

show a deviation of \hat{G} to the left of its expected direction. This is the more usual effect of the sitting or standing posture. In three cases, the gradient lay more than 5 degrees to the right of its expected position, but only Case 12 shows a discrepancy of more than 10 degrees. This was an example of a dropped heart, $\hat{S}A_{QRS}$ apparently pointing backward and upward. This subject, a medical student, had a clear history of bronchial asthma in childhood, and although the discrepancy is only about 11 degrees, it is evident that further study of such cases is required. Master's cases of emphysema show an apparently abnormal deviation of \hat{G} to the right.

Since the hearts of persons with a small A_{QRS} cannot be strongly rotated, the anatomic axis, H, and \hat{G} should not be widely separated, except that, as explained, \hat{G} may sometimes lie even 30 degrees to the left

of its expected position when the subject stands, or even sits up. Note how this close correspondence of H and \bar{G} in the nonrotated heart holds good for Master's cases 17 *A* and *B* and 20 *A*, and our subjects 3, 8, and 12. It may be noted that, as expected, most of the apparently more strongly rotated hearts do not show this close relationship between the anatomic axis and \bar{G} .

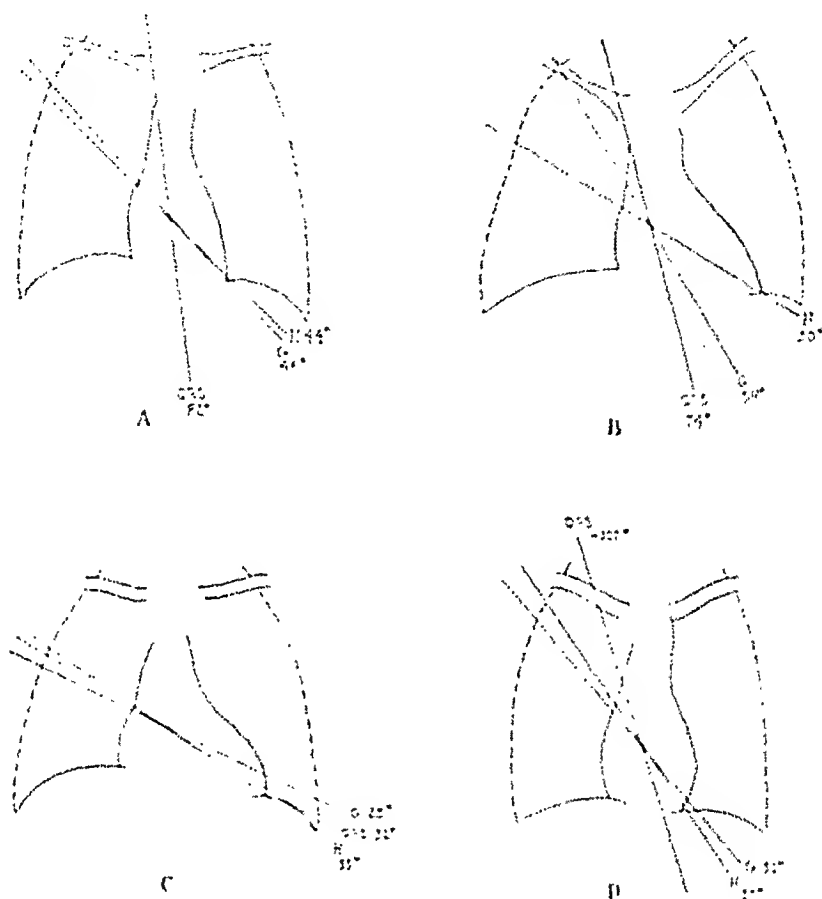


Fig. 5.—*A* and *B* are from the roentgenograms of our Subjects 8 and 10, respectively, of Table II. *C* and *D* are reduced from orthodiagrams of our Subjects 11 and 12.

Case 2 is noteworthy, since it shows that one of the more "transverse" hearts in our group has slight right axis deviation, Λ_{QRS} being plus 90 degrees. But this heart is apparently rotated strongly in a clockwise direction about H , as shown by a deep S_1 and a distinct, although not deep, Q_1 . There was no Q_2 or S_2 . In Case 9, the clockwise rotation at first seemed questionable. By construction from the electrocardiogram of the vectorcardiogram of Wilson and Johnston,² it was easy to demonstrate a distinct clockwise rotation which may be described as moderate. When it becomes possible to ascertain the rotation by the vectorcardiogram, to assess more accurately the effect of rotation about a transverse axis, and to ascertain the magnitudes, Λ_{QRS} and G , with greater pre-

cision, it is not impossible that the normal ranges of deviation between the axes will be found to be less than the methods available to us now indicate.

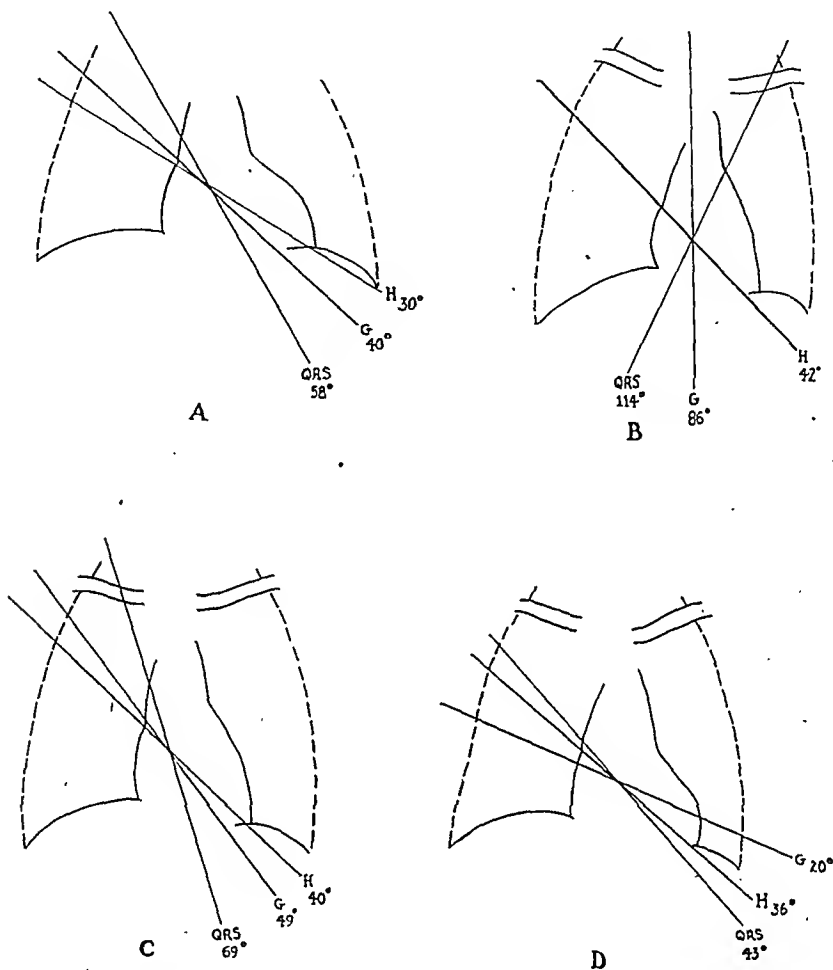


Fig. 9.—A, B, C, and D are from orthodiagrams of our Subjects 13, 14, 16, and 15, respectively, of Table II.

On the whole, however, the series is satisfactory, although the discrepancies are a little greater than in the series from Master's book. With the questionable exception of Subject 12, all fall easily within the ranges for normal subjects we have published previously. This study emphasizes the point that the electrocardiogram which is taken with the subject in the standing or sitting position may be less trustworthy than the one taken when the subject is recumbent. In a later paper we intend to publish a series of electrocardiograms, which had been interpreted as within normal limits by one of us, but which fall outside the usual range as shown by this study.

In reviewing all the normal cases of Tables I and II, it may be of interest to compare the anatomic axes and the gradients of the counter-clockwise and clockwise rotated hearts. As shown by the electrocardiogram, fifteen hearts were rotated counterclockwise about H. The aver-

age anatomic axis is at plus 35 degrees, the average gradient is at plus 18 degrees, and the average \hat{A}_{QRS} axis is plus 4 degrees. There are twenty-nine clockwise rotated hearts, excluding the younger children. The average H is at plus 42 degrees, the average G is at plus 57 degrees, and the average \hat{A}_{QRS} is at plus 74 degrees. Although the anatomic axis of the latter group is only 7 degrees to the right of the former, the gradient is 39 degrees to the right, and \hat{A}_{QRS} , 70 degrees to the right. These average differences may tend to emphasize the contrast between the two groups, and to show how definitely rotation affects the direction of the gradient, and also how extreme is its effect on \hat{A}_{QRS} . There can be little doubt that lack of appreciation of these effects, and the apparent, although not real, discrepancy between anatomic position and the mean QRS axis have been a strong influence in the present tendency to deny the validity of the Einthoven triangle method of ascertaining the directions of the vectors. Although the fact that rotations of the heart about its longitudinal axis affect the electrocardiogram has long been known, the extent of its effects has not been generally appreciated, nor has the effect of rotation of the heart about its transverse axis been generally recognized.

5. *The Position of the Gradient (in Three-Dimensional Space) With Reference to the Ventricular Chambers.*—If we think of SG , the ventricular gradient oriented in three-dimensional space, as a vector longer than the ventricles, and pointing from its electrically negative to its positive pole, we can visualize it as entering the ventricles near the margin of the right ventricular basal border, just below and to the right of the root of the pulmonary cone. It would then pass through the right ventricular chamber, and through the septum not far from its basal margin; thence it extends through the chamber of the left ventricle to emerge from that ventricle near the anatomic center of its free wall. In contrast, the QRS axis would seem to enter the ventricles a little toward the apex from the center of the free right ventricular wall, and to emerge at a point slightly toward the base from the center of the free wall of the left ventricle. Of course, the plane in which each vector lies may be in front of, or behind, above or below, the one indicated, although it seems probable that the vectors will pass through the heart not far from the center of the muscle mass. In support of the suggested three-dimensional orientation is the configuration of the QRS-T complexes observed in precordial leads (Deeds and Barnes).² Typically, in adults under resting conditions, the QRS complex, as recorded from the anterior surface of the right ventricle, not far from the apex, consists of a narrow, usually rather low, R wave, and a deep, much wider, S wave. The $S\hat{A}_{QRS}$ is evidently pointing away from this thoracic point, and this remains true when the area of the QRS is corrected for the potential change of the "indifferent" galvanometer contact. The QRS complex in the anterior axillary or midaxillary lead, on the other hand,

shows that the mean QRS axis points toward those thoracic regions. In contrast with the mean QRS area, is the area, QRS-T, after correction is made for the potential change at the other galvanometer electrode. At the same point over the right ventricle, the net area is positive, and this is likewise true at CF_5 and CF_6 . In adults, therefore, all of these points are usually in the positive field of $S\hat{G}$. When the chest electrode is moved upward, or toward the right, however, to about the basal margin of the right ventricle, the net QRS-T area is negative. In the right axilla, and over the right scapula, for example, the area is strongly negative. This comparison of QRS and QRS-T strongly supports the conclusions drawn from a study of the limb lead electrocardiogram. The reason for the direction of $S\hat{A}_{QRS}$ is given in the paper by Gardberg and Ashman.⁴ The reason for the different direction of $S\hat{G}$ must await an explanation of the physiologic or physical factors responsible for the production of the gradient. After sufficient digitalis administration, which may eliminate the gradient, the net QRS-T areas may become zero in both precordial and limb leads.

There is no need to conclude, from the foregoing facts, that the right ventricle makes any important contribution to the ventricular gradient, although that is possible. A contribution appears to be made either by the interventricular septum or by the right ventricle, or by both, however. We suspect the septum is the more important under usual conditions.

6. *The Probable Error in Vector Direction.*—One gains the impression from a comparison of such contrasting records as numbers 5, 6, 7, 12, and 23 *B* from Master's series, on the one hand, and his numbers 9, 10, and, especially, 26 *B* and 78, on the other hand, that the directions of the vectors as indicated by the electrocardiogram are substantially correct. This agrees with the conclusion of Wilson and Johnston,⁷ and of Gardberg and Ashman.⁴ Yet there is one conclusion we have drawn from our data, consideration of which counsels caution. This is the conclusion that the $S\hat{A}_{QRS}$ may point not only straight backward, but even backward and upward. With the data at our disposal, it is quite impossible to decide whether, as in our Case 8, from a perfectly normal male with no history or indication of either cardiac or pulmonary disease, the apparent direction of $S\hat{A}_{QRS}$ is the true one. In attempting to explain the direction of the vector, several possibilities suggest themselves.

a. The apparent upward and backward direction may be the true one, and be due to an unusually early activation of the anterior wall of both right and left ventricles, as in one of Harris' monkeys. Alternatively, an unusually large, upwardly and forwardly directed component from the pulmonary conus may produce the same effect, although this seems unlikely.

b. The apparent direction may not be the true one. It may be supposed that, particularly for vertically placed hearts, transversely oriented vectors may have less effect on the electrocardiogram than longitudinally oriented ones for reasons which are under discussion and not understood. If, for example, the R-wave vectors point relatively transversely, they may be reduced in magnitude. If, at the same time, the S vectors point nearly vertically upward, parallel to the mediastinum, they may be little affected. The effect would necessarily be to cause an apparent upward and backward deviation of $S\hat{A}_{QRS}$. So far as we can tell at this time, a dubious effect of this sort may often cause an apparent backward deviation of the vectors, both $S\hat{A}_{QRS}$ and $S\hat{G}$; but only much further work, with adequate oblique and lateral views of the heart, will make possible an answer to this question. Whatever the ultimate answer may be for the normal thorax, we can at this time state that in pulmonary emphysema, if the heart is relatively vertical, there is often an apparent reduction in the transverse electrical components of the vectors, with a consequent lessening of the estimated spatial angle between $S\hat{A}_{QRS}$ and \hat{G} .

SUMMARY AND CONCLUSIONS

This study has indicated that:

1. The spatial angle separating the mean spatial QRS axis ($S\hat{A}_{QRS}$) and the ventricular gradient ($S\hat{G}$) is approximately 30 degrees.

2. The angle between $S\hat{A}_{QRS}$ and the longitudinal anatomic axis (H) is about 90 degrees.

3. The angle between H and $S\hat{G}$ is about 60 degrees.

4. When the normal subject is supine, these axes appear to lie very nearly in the same plane; but when the subject stands or even sits up, \hat{G} often shows an apparent counterclockwise rotation about an antero-posterior axis, that is, it seems to deviate to the left. It may also deviate about a transverse axis, but we have no present evidence of this.

5. When the heart is definitely rotated counterclockwise on its long axis, both \hat{A}_{QRS} and \hat{G} lie to the left of the anatomic axis, but \hat{G} lies to the right of \hat{A}_{QRS} . When the heart is definitely rotated clockwise, both \hat{A}_{QRS} and \hat{G} lie to the right of H, but \hat{G} points to the left of \hat{A}_{QRS} (Fig. 1).

6. In normal subjects in the supine position, the observed \hat{G} should probably not deviate by more than plus-minus 15 degrees from the direction predicted from the type of rotation, the directions of \hat{A}_{QRS} and H, and the magnitude, λ_{QRS} .

7. In normal subjects, in the sitting or standing position, \hat{G} may deviate as much as 25 or 30 degrees to the left from its predicted direction (that is, it may be rotated that much counterclockwise about an antero-

posterior axis), and tachycardia may possibly also cause similar deviation on occasion. On the other hand, in this position, \bar{G} should not deviate more than 15 degrees to the right of its predicted direction.

8. When the net manifest area of QRS is small, and either positive or negative, the criteria indicated above must be applied with caution. In such cases, \bar{G} normally seems to lie within less than 10 degrees of \bar{H} in the recumbent subject.

9. The average magnitude in men of the mean spatial QRS vector (SA_{QRS}) is nearly 11 units (1 unit = 4 microvolt-seconds). It is probably slightly smaller in women, and it is presumably still smaller in infants and young children. (A later, mathematical calculation, made after this paper was written, indicates a true SA_{QRS} of very nearly 11.5 units in adult males.)

10. The directions of $S\hat{A}_{QRS}$ and $S\hat{G}$ are estimated in relation to the muscle masses of the ventricles.

It should be pointed out that our proposed limits are tentative. Much more work must be done before the limits can be fixed with precision for all types of subjects.

Excepting the cases of emphysematous or deformed thoraxes, or of the presence near the heart of air, fluid, or consolidations, we believe that the directions of the electrical axes, as projected on the frontal plane, are correct, probably within plus-minus 10 degrees in most cases. In this we agree with Wilson and Johnston.⁷ It is suggested that, in some instances, extreme rotation of $S\hat{A}_{QRS}$ backward may be due to unusually early depolarization of the anterior ventricular walls, as in one of two monkeys studied by A. S. Harris;³ and in other instances, pulmonary changes, perhaps even subclinical in degree, may produce a similar effect.

We are indebted to Dr. James L. Gouaux for drawing the orthodiagrams on eight of our eighteen subjects, and to Mr. W. B. Stewart and Mrs. Harriet Gregory Lawrence for preparation of the figures.

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THE NORMAL HUMAN VENTRICULAR GRADIENT

IV. THE RELATIONSHIP BETWEEN THE MAGNITUDES, A_{QRS} AND G , AND DEVIATIONS OF THE RS-T SEGMENT

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DEVIATIONS of the RS-T segment, so called, are produced usually by one of two wholly distinct mechanisms. One type of deviation or displacement is a normal physiologic phenomenon, related to the relative magnitudes of the manifest mean area of the QRS complex and of the ventricular gradient, and produced by repolarization of the muscle. The second type of deviation is never a normal phenomenon under the conditions obtaining in the human heart, and is related either to abatement, or reversal in the direction of flow, of a current of injury, or to intramuscular blocking of the wave of excitation, or to a combination of both factors.¹ Examples of this second type are usually observable in the electrocardiogram of recent myocardial infarction or of acute pericarditis. It is as yet uncertain whether the segment displacements regarded as characteristic of coronary disease, when induced in the patient by anoxia or exercise, should be classified in one or the other or in both categories, or whether it may not ultimately be necessary to include a third mechanism. This will be considered in the discussion. In any event, it is clear that no aspect of electrocardiographic interpretation is in greater need of sound theoretical analysis than the changes just mentioned. It is the purpose of this paper to analyze the first category of RS-T segment shifts. Not only is this a matter of great practical importance in itself, but, also, it is only in the light of such analyses that trustworthy interpretation of segment changes in general will become possible.

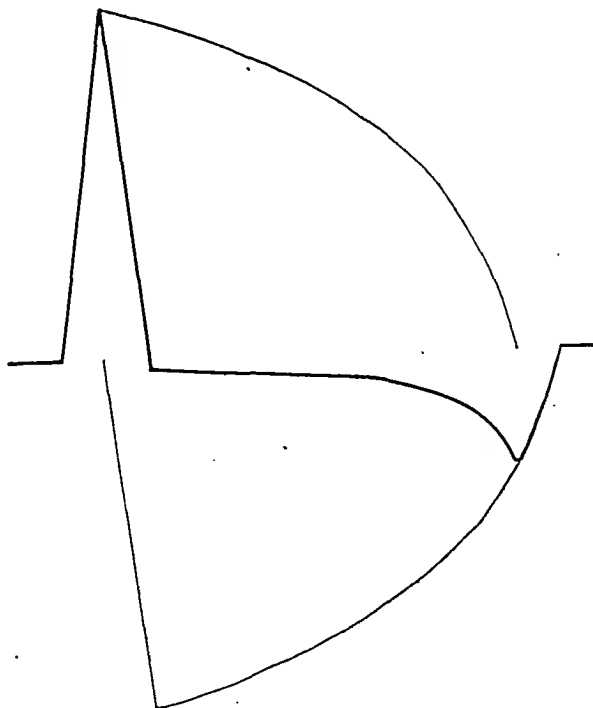
Theoretical Considerations.—One school of German cardiologists has attempted to explain the human electrocardiogram in each lead as the sum of two oppositely oriented monophasic action currents.² Hoff, Nahum, and their collaborators³⁻⁵ have recently made a similar effort. According to the latter authors, one monophasic curve represents the electrical activity of one ventricle, the other, that of the other ventricle, and the two summate to give the "bi-cardiogram." Quite aside from other objections to their view, it was pointed out that the interpretation of the electrocardiogram in this fashion is a serious oversimplification of the total situation.⁶ But it was also stated that, as an approach to certain

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problems, the method has advantages. If used with full realization of its limitations, it affords the most easily understood approach to the problem of RS-T segment deviations of the physiologic type.

Mechanism of Production of RS-T Segment Deviation.—In Fig. 1, two monophasic curves are illustrated. The two are summed algebraically to yield the diphasic curve, consisting of the upright R wave and the downwardly directed T wave.⁶ To take a specific example of what the figure may represent, let us imagine that the diphasic curve is one recorded in a precordial lead from opposite the wall of the left ventricle. Then, disregarding the right ventricle and septum, the upper monophasic curve would represent, very diagrammatically, of course, the time course of depolarization (upstroke of curve) and repolarization (downstroke of curve) of the endocardial surface of the muscular wall of the left ventricle. Since the depolarization does not involve this whole surface simultaneously, the upstroke of the curve is represented as not being very steep. The lower monophasic curve similarly represents the time course of depolarization and repolarization of the epicardial muscle surface. Its electrical effects are opposed to those of the endocardial surface, and, therefore, the direction of the curve is opposite. The lower curve begins later than the upper curve because the epicardial surface is activated later than the endocardial.

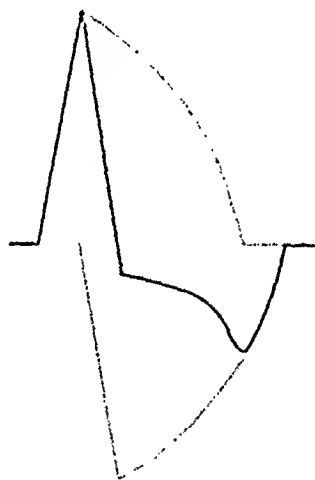


1A

Fig. 1A.—As explained in the text, the two monophasic curves of the same form, one upright and one inverted, summate to give the diphasic curve shown by the heavier line. Since repolarization of the muscle surface responsible for the upper monophasic curve has begun before the downstroke (depolarization) of the lower curve is complete, the RS-T segment is deviated downward, or "depressed." This is an example of what is called a "repolarization or regression deviation" of the RS-T segment in this paper. In this illustration, the heart rate is low.

The form of the part of each curve representing repolarization was experimentally ascertained.⁵ It is a simple logarithmic curve (or very nearly so). Knowledge of its form and the effect of the heart rate upon it enable us to draw all the curves consistently. Actually, since the activation of neither muscle surface is everywhere simultaneous, the repolarization will be rather slower than as indicated, particularly at the end of the monophasic curve.

In drawing Fig. 1, it was assumed that the time course of depolarization and repolarization of the two muscle surfaces was precisely the same. As a matter of fact, in digitalized hearts, such a condition is approximated. Inspection of the diphasic curve shows a moderate *depression* of the RS-T segment. The mechanism of production of this depression is very clear. Repolarization of the subendocardial surface has gone forward before depolarization of the epicardial muscle surface is complete. This is the explanation of RS-T segment deviations of the first type, although the question as to which surfaces are actually involved is still open. In the author's opinion, this interpretation is no longer open to serious doubt.⁵



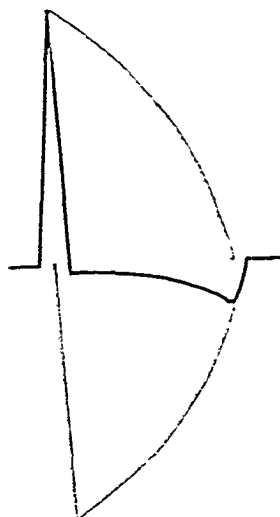
1B

Fig. 1B.—This is like the curve of Fig. 1A but it shows the effect of earlier acceleration, which shortens the duration of the monophasic curve and increases the rate of repolarization. The differences in heights of the curves would not occur with acceleration, and is for convenience in drawing the diagram. Note the marked increase in the "depression" of the segment, in spite of the reduction in the area of the "R wave."

Obviously, if the initial deflection, R, had been directed downward, the segment deviation would have been upward, that is, the segment would have been *elevated*. Therefore, segment deviations produced in this manner (associated, as we shall see, with a reduction in the magnitude of the gradient) are always opposed in direction to the chief initial deflection, R or S. The situation when R and S are equal is considered below.

Effect of Minute Heart Rate Upon the RS-T Segment.—In our experimental work it was shown that when the heart rate is accelerated, the

monophasic curve has a swifter descent initially; the form is close to that shown in Fig. 1B. Its total duration is, of course, decreased.⁵ In this curve, we assume that the time required for full excitation of the surfaces, and for penetration of the ventricular wall by the impulse is the same as in Fig. 1A. It will be observed that the RS-T segment depression is much more pronounced after cardiac acceleration. The T wave has become deeper. Yet, as Wilson, et al.,⁹ have emphasized, the area of R above the line is still equal to the area RS-T and T below the isoelectric or base line. (Since the beating heart moves with reference to the galvanometer leads between the inscription of R and T, this very precise equality would not necessarily be noted, even if one could fully eliminate the ventricular gradient.)



1C

Fig. 1C.—The height of the R wave is the same as in Fig. 1B, but its width is much less and its area is accordingly much reduced. Note that the RS-T deviation is only about one third as great as in Fig. 1B, although the rate of repolarization is the same.

Effect of Reducing the Size of the R Wave.—The effect of reducing the width, and, therefore, the area, of the R wave upon the RS-T shift and the T wave is illustrated in Fig. 1C, which should be compared with Fig. 2. In these latter figures, a heart rate intermediate between the other two is assumed. Since in Fig. 1C the area of R above the line is equal to the area of T (including the RS-T deviation) below the base line, reducing the area of R automatically decreases the area of T. And, of course, increasing R, as in Lead I in left bundle branch block, automatically increases the area of T. (We here neglect the ventricular gradient.)

The RS-T Segment When the Initial Deflection is Diphasic.—In Fig. 1D, we may imagine that the precordial lead wire is moved to a position which gives an R and an S wave that are precisely equal in area. The R is produced by a wall nearer the electrode: the S is caused by the wave of excitation moving away from the chest lead contact into walls

more remote from the chest surface. The lower, inverted RS-T and T are as in Fig. 1A, and correspond to the R of that figure. The upper, upright RS-T and T would follow an equally large S. In this figure, R and S partly combine, so that the area of each is reduced. By summation, the RS-T segment and diphasic T wave shown by the solid line would follow the diphasic initial deflection, R and S. Since the lower curve begins before the upper one, the summated curve will show very slight depression of RS-T. This slight depression may sometimes be large enough to be observed in the human record, as after full or excessive digitalization, with abolition of the gradient.

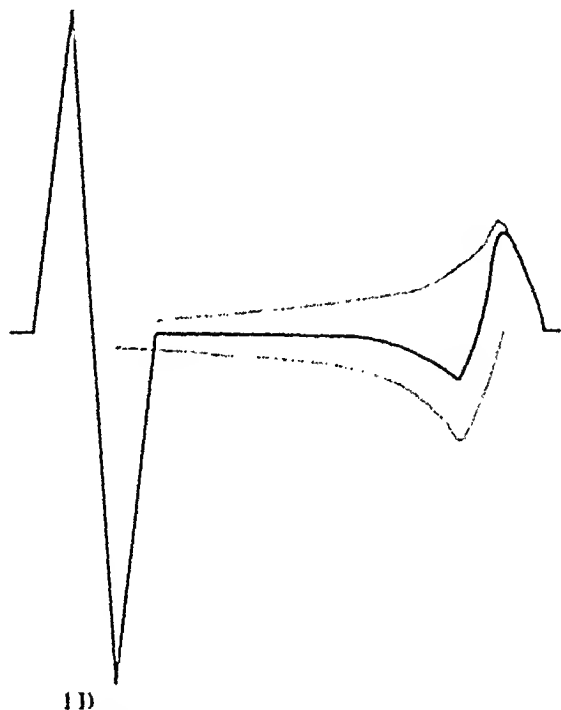


FIG. 1D.—The middle curve shows the form of the RS-T segment and T wave when R and S waves of equal size are present.

The Effect of the Gradient Upon the RS-T Segment.—With the exception of some digitalized hearts, one rarely observes a human heart which does not possess a ventricular gradient. The gradient was defined and experimentally demonstrated by Wilson and his coworkers,^{12, 13} and has been studied in the previous papers of this series.^{12, 24} Although it was suggested that the presence of the gradient results from different time courses of repolarization of different cardiac surfaces or regions, this is not the only conceivable explanation,¹⁵ although it seems to be the most probable one. In view of our ignorance regarding the cause of the gradient, in Fig. 2, A, a quantity representing the gradient is not added by changing the duration of the two monophasic curves, as might be done. Instead, following the R wave, a T wave of approximately normal form and size is arbitrarily drawn in. If we take this ventricular

complex, R and T, to be from one limb lead, then the electrical effect of the gradient, as projected upon the line of the lead, will be equal to the area between the lower RS-T and T curve, and the upper T curve, that is, to area T' plus area T, as shown. Since the area T' (the inverted T) equals the area R, then, by substitution, we see that area R plus area T (the upright T) equals the projected area or value of the gradient. Similarly, the area can be measured in another limb lead, and, from the two lead values, the direction and manifest magnitude of the ventricular gradient, as projected on the frontal plane, can be ascertained, as our previous papers explained.¹²

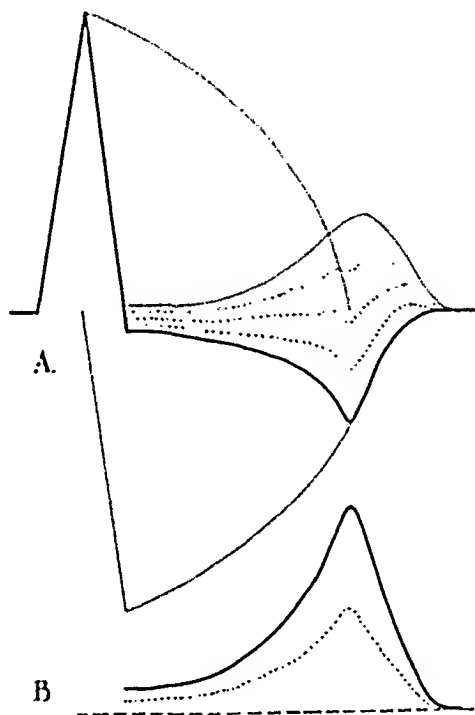


Fig. 2.—A, The lower RS-T segment and T wave are those produced when the heart rate is intermediate between the rates of Figs. 1A and 1B. A T wave of approximately normal form is drawn in arbitrarily. As explained in the text, curve B of this figure is the electrical effect of the ventricular gradient as projected on the lead line. It is derived by plotting the vertical distances between the lower and upper RS-T segments and T waves. The dotted lines represent the effect of reducing the magnitude of the "gradient" by (a) 25 per cent; (b) 50 per cent; and (c) 75 per cent. Note how these reductions influence the deviation of the RS-T segment, and how the gradient may "elevate" the segment. The "gradient" corresponding to the middle dotted line in A is shown by the dotted line in B.

If, at each instant in time, one measures the vertical distance between the profile lines of T' and T, and plots them as in Fig. 2, B, it is evident that the curve of Fig. 2, B, shows the temporal development and magnitude of the potential differences from whose sum in two limb leads the ventricular gradient can be found. The curve has the appearance of an isolated, and, in this case, rather high, T wave.

It should be clear from our discussion, so far, that if R and S were negligibly small, and the T wave were relatively very large in a normal human heart, the T wave would give directly the form and magnitude of the ventricular gradient as projected on the line of the lead. But

such electrocardiograms, from normal subjects, are difficult to find, although they may be closely approximated. The form shown in Fig. 2, *B*, is close to that which is observed. Before the QRS complex is completed, the gradient has already begun to develop, and its rise opposes the depression of the RS-T segment. Depending upon conditions, the gradient may overbalance the RS-T depression, so that an actual elevation of the segment appears, as shown in Fig. 2, *A*; it may simply fully offset the depression; or it may fail to compensate for the depression, and some depression appears.

The Effect of Changes in Gradient Magnitude Upon the RS-T Segment.—Also in Fig. 2, *A*, are shown (dotted lines) the effect of reducing the gradient amplitude (a) by 25 per cent; (b) by 50 per cent; and (c) by 75 per cent. The form of the gradient is assumed to be unaffected. The QRS (R) remains essentially unchanged, except to the slight extent that the beginning of the development of the gradient potential difference affects it. It will be seen that the 50 per cent reduction produced a notch in the T wave (middle dotted line in Fig. 2, *A*). Remarkably enough, such a notch is not at all uncommon, especially in the precordial lead, although it is usually not so sharp, probably because of the temporal dispersion of the potential changes in different regions. However, equal gradient reductions may occur without notching, and notching, of course, may possibly occur without reduction in gradient magnitude. It is likely that the time relations between T' and T differ from heart to heart. This is something which can, at present, be only inferred. It is interesting that in thyrotoxicosis, which will produce a sharper T' (Fig. 2, *A*), notching of the T wave is not uncommon. In this connection, it should be noted that forms of the T shown in Fig. 2, *A*, should be looked for only in leads which show a fairly large R (or S) wave, with the other wave, S (or R), absent or small. Otherwise the situation is complicated, as Fig. 1*D* shows. It is evident that an analysis of the T wave along these lines necessitates careful examination of thousands of electrocardiograms and a careful consideration of factors which are not relevant to the present paper, together with a more thorough analysis than is here required.

It should be emphasized again that our diagrams are oversimplified, in contrast to the conditions obtaining in the whole human heart. The analysis applies primarily to those leads which possess a QRS complex which is mainly unidirectional, but it may also be applied more generally to the three leads of any electrocardiogram, as shown in the next section.

Evidence From the Human Electrocardiogram.—In a previous paper of this series it was demonstrated that augmentation of the heart rate was associated with a decrease in the magnitude of the ventricular gradient.¹⁷ In the foregoing sections it has been shown that an increased net area of the QRS should be associated with an increased de-

viation of the RS-T segment. It was also shown that, with the net QRS area constant and no gradient present, slowing of the heart should *lessen* the extent of the RS-T segment shift, and vice versa.

In order to test the correctness of these theoretical expectations, twenty-eight electrocardiograms showing some degree of S-T segment "depression" were chosen at random. By "depression" is meant a deviation opposite to the direction of the chief QRS deflection, as in our illustrations. To these twenty-eight records were added, also at random, nine electrocardiograms which revealed no shift, and thirteen with slight "elevation" of the segment, namely, a deviation in the *same* direction as the direction of the chief initial QRS deflection. Various clinical conditions were represented, but care was taken to exclude all records which might show shifts belonging in the second category, as stated in the introduction. Electrocardiograms showing high P waves were excluded because of the frequent difficulty in correcting a segment shift when the end of an auricular T is superposed. The total number of electrocardiograms studied was fifty. Although small, the series proved fully adequate for our purpose, as the reader may judge for himself from Table I.

TABLE I

RS-T SEGMENT DEVIATIONS IN THE ELECTROCARDIOGRAMS OF FIFTY PATIENTS

G/A _{QRS} < 0.9				G/A _{QRS} = 0.9 to 1.5				G/A _{QRS} > 1.5			
A _{QRS} LARGE	A _{QRS} SMALL	A _{QRS} LARGE	A _{QRS} SMALL	A _{QRS} LARGE	A _{QRS} SMALL	A _{QRS} LARGE	A _{QRS} SMALL	A _{QRS} LARGE	A _{QRS} SMALL	A _{QRS} LARGE	A _{QRS} SMALL
RATE	RATE	RATE	RATE	RATE	RATE	RATE	RATE	RATE	RATE	RATE	RATE
HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW
-1.00	-1.20	-0.82	-0.45	-1.00	-0.20	-1.00	-0.45	-	+0.80	+0.40	+0.55
-1.00	-0.50	-0.80	0	-0.85	0	-0.55			+0.60	+0.30	+0.42
	-0.45	-0.40		-0.70		-0.45			+0.33	0	+0.40
	-0.33			-0.60		-0.35			0	0	+0.40
	-0.25			-0.35		0				-0.10	+0.30
				-0.30						-0.22	+0.30
				-0.20							+0.10
											0
											0
											0
											0
											-0.10
											-0.33

Note: A minus sign means that the manifest magnitude of the deviation, in millimeters (0.1 mV), is opposite to the direction of the chief deflections of the QRS complex. A plus sign means that the deviation is in the same direction.

In the case of each electrocardiogram, the manifest magnitudes of the net QRS areas (A_{QRS}) and of the ventricular gradient (G) were ascertained,¹² and the directions of A_{QRS} and G were also calculated. If any deviation of the RS-T segments was present in the limb leads, the manifest magnitude and approximate direction of the deviation were ascertained. In this connection it should be pointed out that when, as in left ventricular hypertrophy and left axis deviation, RS-T is depressed in Lead I and elevated in Lead III, as is so frequently the case, it is wholly fallacious to summate the deviations in the three leads in order to esti-

mate the magnitude of the deviations. For example, suppose the deviations are respectively minus 1.00 mm. and plus 1.00 mm. in Leads I and III. The direction of the shift is then plus 150 degrees, and the manifest potential of the shift is 1.15 mm.¹² The current practice of adding the magnitudes of the deviations in the three limb leads, without consideration of associated factors or of the true manifest magnitude of the shift, can only lead to confusing and unreliable results. Even though, in practice, the method has been of some value, it could be made more valuable if the problem were approached scientifically.

Since a large net QRS area, other things being equal, produces a large RS-T shift in the absence of a gradient, it is evident that we can not make a simple comparison of that area and the shift. To offset a large RS-T depression after a large R, a proportionately large gradient is required, and, vice versa, a proportionately small gradient will offset the depression after a small R. For this reason, to make the analysis valid, the manifest area of the ventricular gradient, G , was divided by the mean manifest area of QRS or A_{QRS} , in each case. In Table I the fifty electrocardiograms are divided into three groups: in one, the ratio, G/A_{QRS} , is below 0.9; in the second, the ratio is 0.9 to 1.5; in the third, the ratio is over 1.5. (The usual ratio, at ordinary heart rates, averages slightly over 2.0.)

Each of these groups was then subdivided into two, one with an A_{QRS} of 8.0 units (32.0 microvolt-seconds), or above, the other below 8.0 units.¹² The reason for this subdivision can be made clear as follows: When the ratio, G/A_{QRS} , is large, no segment depression is to be expected in either case. But if the ratio were 0, that is, if a gradient were absent, then, as shown in the theoretical discussion, the segment shift will be larger when A_{QRS} is large than when it is small. Similarly, therefore, any decrease in gradient magnitude will produce a proportionately greater depression in the presence of the larger A_{QRS} value. Even though the number of cases is small, the figures in the table fully justify this subdivision, and experience also demonstrates that the largest deviations occur in the presence of large A_{QRS} areas.

A further subdivision separated each subgroup into those in which the heart rate was over 85 and those with rates of 85 or less. This was necessary because, as we have seen, an increased rate produces a greater RS-T depression, and a relatively large gradient is, therefore, needed to offset it.

As inspection of the table demonstrates, the hearts with large A_{QRS} values, rapid rates, and smaller G/A_{QRS} ratios have, on the average, the greatest manifest RS-T depressions; whereas the hearts with smaller A_{QRS} values, slower rates, and larger G/A_{QRS} ratios show fewest RS-T depressions and the greatest number of elevations. In every detail, the results of this study of the human electrocardiogram are in accord with the theoretical explanations we have given.

The larger segment deviations were practically opposite in direction to the mean QRS axis. This is also in accordance with theoretical expectation.

It is purely a matter of chance that the manifest magnitude of the RS-T deviation did not exceed 1.2 mm. in any of our cases chosen at random. In rapid hearts with large QRS areas and small gradients, the shift may often exceed this figure. Even in quite normal hearts, under certain conditions, large deviations may be observed. In Fig. 6 of the second paper in this series,¹³ from a normal student while standing, the manifest magnitude of the depression is about 1.5 mm., after allowance for an auricular T wave. The electrocardiogram from the same student, taken in the supine position, shows a clear depression, especially of RS-T₃, which is due to the large R wave area, to a relatively small gradient, and to a rather large angle (as explained below) between the vectors, \hat{A}_{QRS} and \hat{G} . Electrocardiograms of this type are not very uncommon. They emphasize the purely physiologic nature of this type of deviation.

The Effect of the Projection of the Gradient Upon the Line of the Lead of the Electrocardiogram.—In the foregoing discussion, it has been tacitly assumed that the directions of the vectors, \hat{A}_{QRS} and \hat{G} , are the same. Actually, of course, as the earlier papers demonstrated, this is rarely true, yet in a majority of electrocardiograms the angle between the two axes is not large, and the effect of their divergence can be neglected. The following general statement of the effect of such divergence is probably the best. If the directions of \hat{A}_{QRS} and \hat{G} , as projected on the line of any of the three limb leads, are the same, the effect of \hat{G} will be to oppose the "repolarization" RS-T deviation, and the magnitude of the opposition will be proportional to the magnitude of \hat{G} as it is projected on the lead line. This statement involves the assumption that the time course of development of the electrical forces giving rise to the gradient is similar in different hearts. On the other hand, if the directions of \hat{A}_{QRS} and \hat{G} , as projected on the line of any of the leads, are opposite, the effect of the gradient will be to exaggerate the "repolarization deviation" (see discussion below), and the degree of the augmentation will be proportional to the magnitude of the projected \hat{G} . Of course, if the direction of the gradient is at right angles to the line of the lead, its magnitude in that lead will be zero, and it will have no effect upon the "repolarization deviation."

Fig. 3, from a syphilitic patient with no clear evidence of heart disease, illustrates this phenomenon. The mean QRS axis is plus 110 degrees and \hat{G} is at plus 57 degrees. As projected on Lead I, \hat{A}_{QRS} points from the left arm to the right arm, and repolarization following the large S should give an "elevation" of the segment. \hat{G} , as projected, points from the right to left arm, and here augments the "elevation" due to repolarization. As projected on Lead II, \hat{A}_{QRS} and \hat{G} are in the same direction, and the effects balance so that no measurable segment

deviation appears. In Lead III, again, the directions are the same, as projected, but G is relatively small in this lead and does not fully offset the "repolarization deviation," and the segment is "depressed." Another example, with left axis deviation in this case, is shown in Fig. 4.

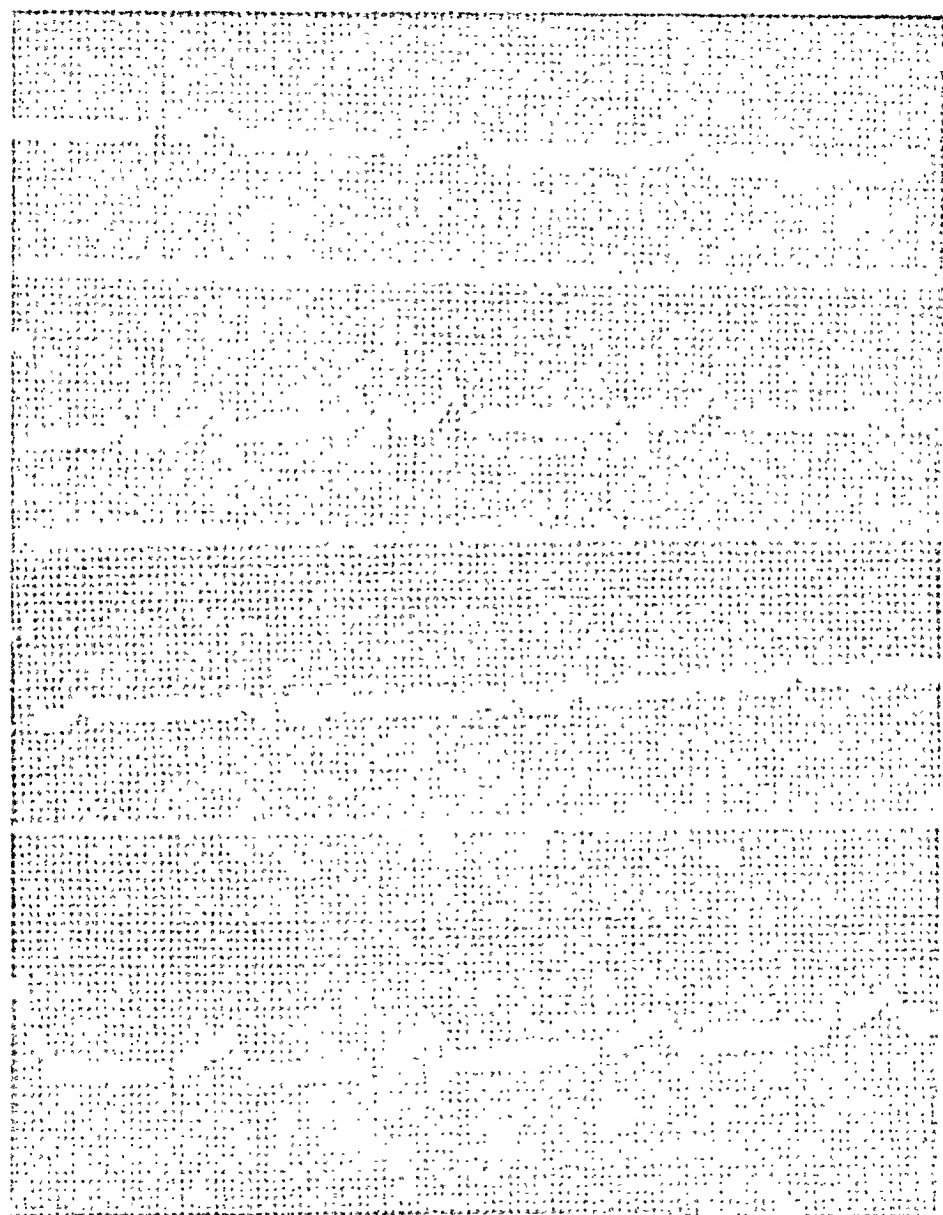


FIG. 5.—Electrocardiogram discussed in text. A 6-lead strip, 26 years old. Wasser-
mann positive. Complaints of pain in right hemithorax and shortness of breath in
morning. Lower curve, Lead IV-V.

The direction of Δ_{QRS} was estimated at minus 27 degrees, and, of \bar{G} , at minus 20 degrees, i.e., nearly the same. In this case the two factors are opposed in all leads, as in most electrocardiograms, but the very large gradient produces an elevation of RS-T, and a depression of RS-T₁.

Figs. 4 and 6 in the second paper of this series show deviations which are mainly due to a relatively small G/A_{QRS} ratio.

Segment Deviations Due to Other Causes.—As explained in the introduction, segment shifts are of two main types: (a) those associated with reduction in the magnitude of the ventricular gradient, and (b) those due to blocking of excitation waves, either in the presence or absence of a current of injury. The latter type has been explained most recently by Bayley.¹

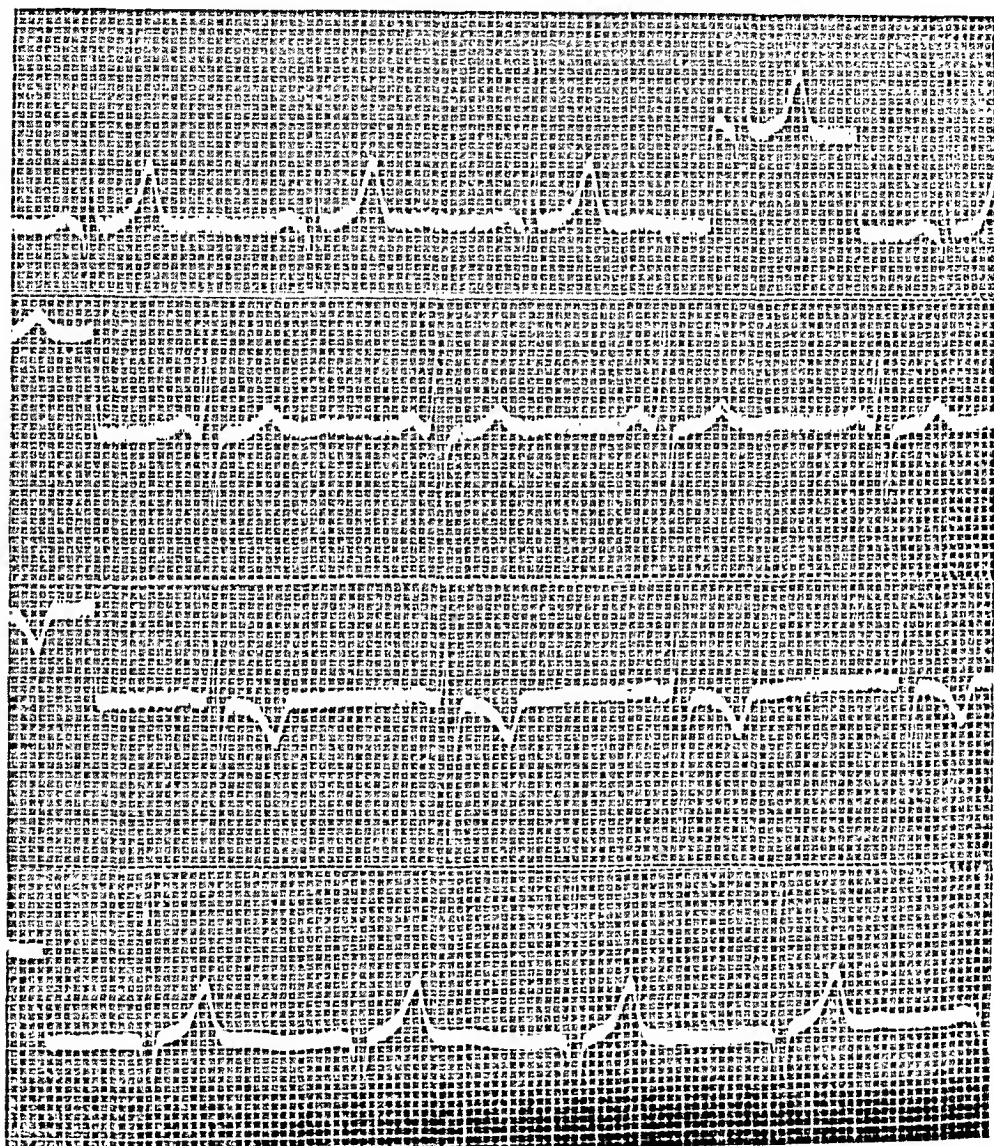


Fig. 4.—Electrocardiogram of a white man, aged 52 years. Admitted to hospital for hernia. No cardiac complaints. Blood pressure reported as 138/100. A_{QRS} , minus 27 degrees; G , minus 20 degrees. Strong counterclockwise rotation of heart on long axis. Since the patient was seated when the electrocardiogram was recorded, it may be within normal limits, although some left ventricular hypertrophy is probable. In 1940, the electrocardiogram was regarded as abnormal. Lower curve, Lead CF .

In addition to these two types of RS-T segment shift, it is possible that a third type exists which can be ascribed neither to diminution in the magnitude of the gradient nor to recent muscle damage. In these cases, the direction of the deviation is like that in the physiologic type, but its

extent cannot readily be explained as the result of a simple reduction in gradient magnitude, for G may be normally large. In my experience, curves of this sort are most frequently observed in middle-aged or older women, and are of the type Scherf and Boyd¹⁶ ascribe to "ovarian deficiency." Since there is no heart disease in many cases, the factors responsible must be physiologic. Most probably this group of shifts is merely a variant of the physiologic type, and it can be ascribed to a slow initial development of the potential responsible for the gradient, or, otherwise stated, to a change in the time course of repolarization of the muscle. The two examples of "depressed" segments shown in the column at the extreme right in Table I were from middle-aged women, and one of these is negligibly small. In the present paper, deviations associated with the large, wide T waves ascribed to myocardial ischemia are not considered. They may possibly require special treatment.

Left Ventricular Hypertrophy.—In left ventricular hypertrophy the deviations commonly observed are purely of the physiologic type. They are, therefore, opposite in direction to the chief initial deflection. If there is a high R_1 and a deep S_2 , the segment is depressed in Lead I and elevated in Lead III. If, as is not very unusual, there is a fairly high R in all three limb leads, and only small S waves, the segment is commonly depressed in all three leads. These relationships have been studied in a large number of cases, and are reasonably consistent. Usually, in left ventricular hypertrophy of significant degree, the magnitude of the ventricular gradient is normal if there has been no left ventricular failure; after, or certainly during, failure, the magnitude, G , decreases as a rule. In the first condition, segment deviations are due to the increase in the area, A_{QRS} . After failure, both the increased A_{QRS} and the reduced G contribute to augmentation of the shift.

DISCUSSION

In the foregoing paragraphs it has been demonstrated that deviations of the RS-T segment of the type not associated with blocking of impulses within the living myocardium are physiologic, and are merely manifestations of the normal and necessary repolarization of the muscle. After digitalization of a patient, the deviations observed are produced by the same mechanism, although digitalis probably not only reduces the size of the gradient, but also modifies the form of the repolarization curve, as well. In failure of the left ventricle, and in some other conditions which also require careful study, the magnitude of the ventricular gradient is often reduced, and repolarization deviations often appear as a result.

No precise limit can be given for the extent of the deviation, since that varies with the net positive or negative area of the QRS complex, with the degree of reduction in the size of the ventricular gradient, and with the heart rate. Digitalis has an effect much like that of cardiac acceleration. Particularly in the precordial lead in left ventricular hy-

hypertrophy, when recorded from a point opposite the right ventricle, the R wave is small and the S wave is often very large. Then either digitalis or an increase in heart rate may produce a deviation upward of the RS-T segment of several millimeters, and the picture sometimes closely resembles that observed after infarction of the anterior left ventricular wall. Similarly, a large R wave in the chest lead may be followed by a depression of the segment like that which occurs with recent infarction of the posterior ventricular wall. This is one reason why the facts herein presented are important.

In using the exercise or anoxia test for coronary insufficiency, an appreciation of the causes of normal deviations is desirable. It is true of the published records (for example, the paper by Twiss and Sokolow¹⁷) that the changes are undoubtedly significant, and not to be explained by a physiologic change that is likely to occur in the normal heart under the conditions given. But in less expert hands, especially when there is considerable acceleration and when the R or S waves are large, a wholly unspecific change might easily be regarded as significant. This is another reason for stressing the facts of this report. Exercise does not often reverse the direction of a T wave of fair amplitude in the normal person, but the T-wave inversions produced by the standing posture in Fig. 6 of a previous paper¹³ are worthy of note.

Another application of the facts of this paper is open to further development. A knowledge of the A_{QRS} area, the gradient magnitude, the Q-T duration (mainly contingent on the heart rate),¹⁸ and the relative directions of \hat{A}_{QRS} and \hat{G} , and a knowledge of whether the patient has received digitalis or not enable one to estimate the approximate magnitude and direction of the expected RS-T segment deviation. If the direction or magnitude of the deviation is not as predicted, or if a deviation is absent when it should be present, then it may become possible to recognize deviations of the second type which may possibly escape recognition by employment of present methods. Obviously, this is a problem which demands much further detailed study.

In conclusion, it may be pointed out again that the names for RS-T segment deviations are unsatisfactory, since they are based upon the superficial appearance of the segment, and take no account of the two entirely different mechanisms of segment production. The names "permanent" and "temporary" have been proposed. But the permanent type, as in left ventricular hypertrophy, is produced by the same mechanism of repolarization as the shifts which appear, for example, on a change from the supine to the standing posture. The shifts due to cardiac acceleration are often more transitory than the deviations due to injury (blocking), which are called "temporary." Better names would seem to be "*repolarization or regression deviations*" for the one type, and "*injury deviations*" for the other. The word injury is used in a broad sense to include any injury or depression of the muscle which is sufficient to block the impulses within the walls. It may be added that in-

traventricular block, as ordinarily defined, does not produce deviations of the injury type, because no intrafiber blocking occurs, or, alternatively, because no current of injury is present.³ The repolarization deviations are practically always opposite to the larger deflection of QRS, providing the deflection is of fair size and is distinctly larger than the other QRS deflection or deflections. It is, therefore, often superfluous, in such cases, to refer to the direction of the shift as a depression or an elevation. The injury deviations (or shifts) may go in either direction. Hence it seems necessary to indicate the direction, and the terms "depression" or "elevation" are satisfactory.

In addition to the names suggested above, a name also seems needed to describe the deviations, such as those shown in Fig. 4, which are due to the presence of a ventricular gradient. However probable, it is not certain that these are a consequence of repolarization. They might be called "gradient deviations."

Certain other aspects of this problem will be considered in a paper on the T wave, which is now in preparation.

SUMMARY

The analysis of any diphasic ventricular complex of the electrocardiogram from the standpoint that it is produced by the summation of two monophasic curves has certain advantages.

By use of this method it is shown that, other things being equal, the extent of deviation of the RS-T segment, in the absence of a ventricular gradient, or of injury effects, is determined by at least two factors:

1. The net area of the QRS complex.
2. The heart rate or, otherwise stated, the duration of the Q-T interval.

The effect of a diphasic form of the initial ventricular complex is considered.

The effect upon the RS-T segment of the presence of the electrical forces which give rise to the ventricular gradient is discussed from the standpoint (a) of the magnitude of the gradient in relation to the magnitude of the net QRS area; and (b) of the magnitude of the gradient as projected on a lead line in relation to the net QRS area in that lead.

It is shown that the RS-T segment deviations observed in human electrocardiograms agree with the theoretical expectations.

It is suggested that RS-T segment deviations of the type described be called "repolarization or regression deviations"; that those produced by injury or muscle depression and blocking be called "injury deviations"; and that the characteristic slight deviations due to the presence of a large ventricular gradient be called "gradient deviations." If it should be found that other mechanisms of segment deviations exist, other categories may be included.

A few clinical applications of these observations are briefly stated.

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ANOMALOUS ORIGINS OF THE POSTERIOR INTERCOSTAL ARTERIES FROM 915 THORACIC AORTAS: THEIR ROLE IN FRACTURES OF THE RIBS

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A NUMBER of years ago, after World War I, the discovery of fractured ribs at post-mortem examination of patients in Massachusetts hospitals for mental diseases led to inquiries of how they were received and whether external force was applied, and, if so, in what manner. These fractures occurred in men almost entirely, were frequently bilateral, and involved the fourth to eighth ribs. The circumstances led to the conclusion that they were traumatic in origin. A staunch clinician held that they were done post mortem, but, in view of the fact that they were attended by free hemorrhage in surrounding tissues, that claim was not substantiated. No thought had at that time been given to the possibility of change in the ribs caused by a reduced circulation, either by anomaly of their arteries, or sclerosis of the aorta narrowing or occluding the origins of the intercostal arteries.

It had been found in 1917, when mental hospitals were short of help because of military enlistments, that the amount of pulling force required to fracture a rib could be ascertained by means of a brass arm and scale devised by a professor at the Massachusetts Institute of Technology. This arm was hooked on to the median tip of ribs isolated by removing their bordering muscles after the sternum was cut away, and the instrument manually lifted. The figures registered on the scale varied from $1\frac{1}{2}$ pound to 18 pounds. In sixteen instances, the ribs were tested by the device mentioned. Eleven of the patients were men and five were women. Their ages were from 24 to 79 years. There were no normal controls because the autopsies were done on those suffering from mental disease or defect. After a time the test was given up because of the press of other inquiries.

The increase in the amount of *pulling* force required in most cases to cause a fracture, as one progresses from the upper ribs to the lower, may have some significance. It takes more force to break a bony circle than an ellipse, which the upper four ribs resemble; moreover, it is more awkward to apply force externally high on the chest than lower, even if it takes more force to fracture the lower ribs. This, together with the greater protection of the upper chest by the arms, may explain why more fractures occur in the lower ribs. Falls against tables, bed frames, chairs, or toilet bowls could hardly reach above the nipple line. Bilateral crushing pressure, applied from behind the patient, or a knee

on a chest, can be effective in a short time, but again such fractures tend to occur in the lower group of ribs.

In the sixteen instances mentioned, the five women were over 70 years old, and it took only $\frac{1}{2}$ pound to 5 pounds to break the ribs from above downward. Five of the men were under 50 years of age, and it took from 2 to 18 pounds to cause a fracture; in the six who were over 50 years of age, $\frac{1}{2}$ pound to 10 pounds were required. In this group the condition of the aorta or the presence of debilitating diseases is too small to be considered.

Campbell¹ used a simple instrument with a stirrup and screw, the turning of which against a convexity and concavity of the eighth rib post mortem would register the breaking strain. The first fact he was able to discern was that it would require 66 pounds of pressure to break the toughest rib, and this amount would lessen, with increase in age and the presence of debilitating diseases. He stated that ribs of women would break at half the strain required for men. He gives a condensed table in his second report,² which is shown in Table I.

TABLE I

	MALES		FEMALES	
	AGAINST THE CONVEXITY	AGAINST THE CONCAVITY	AGAINST THE CONVEXITY	AGAINST THE CONCAVITY
58 Insane	41.04 lb.	42.14 lb.	20.68 lb.	20.90 lb.
58 Sane	42.73 lb.	42.63 lb.	23 lb.	23.3 lb.

This compares the breaking strain of the eighth rib in both sexes of various ages in a series of 58 sane and 58 insane persons. It was Campbell's idea that it was not mental diseases, but the debilities that accompanied them, that made the ribs somewhat more vulnerable, as, for example, tuberculosis and syphilis. He, of course, mentions self-injury in excited periods and rough methods of handling.

Whether "strain" (Campbell), or "pulling force" (Canavan), registered by mechanical means on the dead rib, has any bearing on the amount of trauma presented to the living has apparently not yet been recorded. A simpler way would be to apply the finger and thumb force to the isolated rib.

For years the discovery at autopsy of broken ribs was charged up to the disciplinary methods of the men who were then procurable as attendants.

Dr. Leary's³ observations on the effects of alcohol on the human body surprised many workers when he announced that alcohol, when taken in sufficient quantities to brand a person as an alcoholic, was not responsible for sclerosing the aorta. In other words, an advanced alcoholic had a smooth aorta. Dr. Leary's observations regarding the effect of alcohol on aortas were made in his active service as medical examiner, where he could catch his patients red-handed as to habits. Our aortas were from patients with varying length of residence in mental or gen-

eral hospitals, where time and other factors might disguise the lack of alcoholic effects on the aortas. His observations, however, were a signal to examine carefully all aortas post mortem, and thus the anomalous intercostal branches from the thoracic aorta came to light.

From my own service and from numerous friends engaged in pathologic work in Massachusetts and other states, aortas were received fixed in formalin. It would have been advantageous had all these vessels been flattened against the inner wall of a good-sized round glass jar containing a 10 per cent solution of formalin, thus preventing distortion. However, the good will of the donors offset these difficulties, for they not only saved and sent the specimens, but furnished clinical data, such as hospital and autopsy number for identification, the age and sex of the patient, history or no history of alcoholism, and the presence or absence of syphilis. Particularly am I indebted to Dr. William Freeman, Dr. B. E. Clarke, Dr. Donald J. Henderson, and Dr. I. B. Akerson. A total of 915 unselected aortas were collected.

There were 473 males and 371 females. In the remaining 71 cases the sex was not recorded. Their ages, arranged by decades, are given in Table II.

TABLE II

AGES IN DECADES	NUMBER OF CASES
0-10	17
11-20	11
21-30	23
31-40	78
41-50	96
51-60	143
61-70	191
71-80	191
81-90	68
91-100	5
101-110	1
Unknown	81

Most of the aortas came from those who had attained ages from 31 to 90 years, but there were some from younger persons, even premature babies.

Since no bone or portion thereof could be used as a landmark for the removed aorta, one of the main upper branches of the arch, the subclavian artery, was considered the upper limit, and the diaphragm the lower limit, of the thoracic aorta. The usual procedure, at autopsy, to reveal disease of the aorta is to make a ventral cut from the bifurcation of the aorta to its arch, in situ; in fact, any other approach would be awkward. This leaves the renal arteries, if normal, in a bilateral position as guides to the posterior midline of the aorta, where the paired segmental origin of the posterior intercostal arteries of the thoracic aorta should arise.

Adachi,⁴ in his painstaking work on the human arterial system of 196 Japanese subjects, pointed out that in the fifteen thoracic aortas which he studied there was a deviation to the right or left of the posterior

median line for the origin of the posterior intercostal arteries from the thoracic aorta. It was indicated that these deviations were caused by the rotation of the developing esophagus and aorta in the embryonic period.



Fig. 1.

Fig. 2.

Fig. 1.—Group 1. Paired intercostal arteries arising in the posterior midline of the aorta.

Fig. 2.—Group 1. Same, showing the effect of arteriosclerosis of the aorta on the origins of the intercostal arteries.

This proved to be, for the most part, an excellent way to sort out the types of origins of these same branches from the 915 aortas in the present series. Taking the expected posterior mid-locations of the nine pairs of intercostal arteries first, they were found so placed in 231 instances (25.2 per cent). Of course, there were the inevitable "variations" from this criterion, but if more than half of the branches were so placed in a given aorta, they were classified under Group 1 (Figs. 1 and 2), even though some might appear as a single large or a single small opening in some localities, or present themselves focally in triads.

With the same leeway, Group II (Fig. 3) contains those which, nearest the subclavian, were found on the left of the median line, but deviated to the right of it before the level of the diaphragm was reached.



Fig. 3.

Fig. 4.

Fig. 3.—Group II. Note that upper orifices of the intercostals hold to the left of the central lines; lower pairs to the right.

Fig. 4.—Group III. Here is the reverse of Group II. The upper pairs are on the right; lower ones make their way to the left.

This occurred in 41, or 4.5 per cent, of the cases. Those in Group III (Fig. 4) were in reverse of the latter, i.e., were on the right side nearest the subclavian and migrated toward the left as they descended; this group included 71 cases (7.8 per cent). Those in Group IV (Fig. 5) were much more definitely on the right all the way, and this occurred in 314 instances (34.3 per cent). Those making up Group V (Fig. 6) were all on the left of the median line; of these there were 168 cases (18.4 per cent), or, roughly, half the number which were in totally right-sided placement. The surprise was in Group VI (Fig. 7), which is composed of those showing *anterior* origins of the intercostal arteries,

for this occurred in 75 cases (8.2 per cent). Group VII (Fig. 8) includes those which showed such scattered or miscellaneous origins that they could not be assigned to any of the other groups, elastic as were the criteria for them all. There were 16 such cases (1.7 per cent). Table III presents the origins of the intercostal branchings in the whole series, briefly, in tabular form.



Fig. 5.

Fig. 6.

Fig. 5.—Group IV. The paired intercostal arteries are all on the right of the median line.

Fig. 6.—Group V. Here the paired intercostal arteries are all on the left of the median line.

In 673, or 73.6 per cent, of the aortas, these origins were complicated by atherosclerosis or arteriosclerosis, which narrowed or covered the mouths of the thoracic intercostal arteries.

Alcoholism was known to have been included in the history of 92 of the 915 patients whose aortas were studied; of these 92 the aortas were smooth in but 20 (21.7 per cent). Dr. Leary had said, in a conversa-

TABLE III

PAIRED INTERCOSTAL BRANCHINGS FROM THE THORACIC AORTA IN 915 SUBJECTS

GROUP I	GROUP II	GROUP III	GROUP IV	GROUP V	GROUP VI	GROUP VII
Paired in posterior mid-aortic line.	Upper on left; lower on right.	Upper on right; lower on left.	All on right.	All on left.	All anterior.	Scattered and miscellaneous.
41, or 231, or 25.2 %	41, or 4.5 %	71, or 7.8 %	314, or 34.3 %	168, or 18.4 %	75, or 8.2 %	16, or 1.7 %

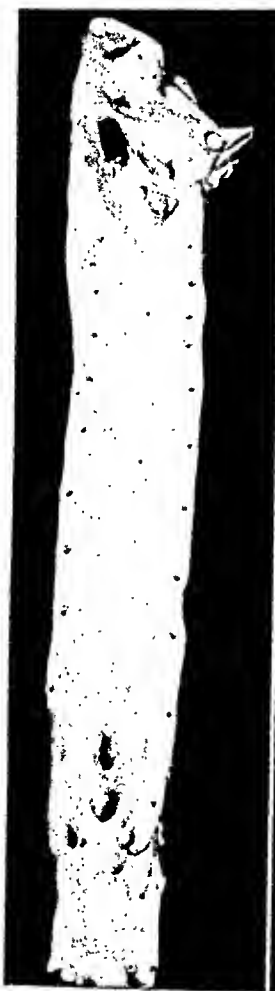


Fig. 7.



Fig. 8.

Fig. 7.—Group VI. This demonstrates complete half swing of intercostal arteries to the anterior wall of the aorta.

Fig. 8.—Group VII. The scattering of origin of intercostal arteries is complicated by advanced sclerosis of the aorta.

tion, that, for the best effect, that is, from the standpoint of smoothness of aortas, the patients would have to be "drunk every day," which he considered "expensive."

Among the 915 aortas, 84 (9.2 per cent) had belonged to patients who were known to have had syphilis, and in 14 of the 84 (16.7 per cent) a tertiary lesion in the aorta was recognized.

From a surgical standpoint the muscular branches of the intercostals are of most interest, for accidental wounds or even carefully planned thoracic surgical procedures may open anomalous branches, with resultant hematomas of various sizes. In the literature, early reports concerning intercostal arteries dealt mainly with hemorrhages from wounds or rupture of these vessels from vertebral caries.

COMMENT

If the ribs, which are among the main sources of erythrocytes,⁵ may be considered to receive their blood supply from the anterior and posterior intercostal arteries, although no textbook which I consulted states this as a fact, the majority of them in this group of 915 cases had handicaps. These handicaps consisted of anomalies of origin of the posterior intercostal arteries in 685 (74.9 per cent) of the aortas, and sclerosis of the aorta contributing to diminished blood supply because of diminishing the size, or sometimes occluding their orifices, in 673 (73.6 per cent). This may be the answer to our original quest for a reason for the perplexing incidence of fractured ribs at post-mortem examination of these patients. They may have had anomalous, or closed, intercostal artery origins.

SUMMARY

Nine hundred fifteen aortas were collected from various hospitals during the years 1934 to 1937. All had been fixed in a 10 per cent solution of formalin, and all but three were believed to have been opened anteriorly. The subclavian artery was considered the upper limit of the thoracic aorta, and the diaphragm, the lower.

Nine pairs of intercostal arteries should arise in the posterior midline of the aorta above the diaphragm. With allowances for variations, this was found to be true in 25.2 per cent of the cases.

In 74.8 per cent they deviated to the right, to the left, or to the anterior wall, or were scattered in their placement of origin, constituting a devious delivery of blood.

In the 915 aortas, 673, or 73.6 per cent, had thickening or destruction of the aortic intima, further interfering with the nutritional function of the branches.

In 84 patients there had been syphilis, and a tertiary lesion was recognized in fourteen, or 16.7 per cent, of the 84 aortas.

Alcoholism was known to have been included in the history of 92 of the patients, and in these the aortas were smooth in twenty, or 21.7 per cent.

I am greatly indebted to Dr. L. Eisenhardt and Dr. H. L. Weatherford for assistance in the preparation of this paper.

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ATRIAL SEPTAL DEFECT

A REPORT OF TWO CASES IN WHICH THERE WAS RECURRENT LARYNGEAL NERVE PARALYSIS

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AN ATRIAL septal defect, occurring either alone or in association with other developmental or acquired defects of the heart, was present in about 8 per cent of the 1,000 cases of congenital heart disease collected by Abbott.¹ It is not the purpose of this paper to review the already extensive literature on this subject, for an excellent summary of previous reports appeared in connection with an analysis of fifty-two additional cases, by Bedford, Papp, and Parkinson.²

The occurrence of an unusual, and apparently rare, complication of this congenital abnormality, together with the fact that patency of the ductus arteriosus was incorrectly diagnosed in one instance and a substernal goiter was suspected in the other, makes the following two cases worthy of a fairly detailed report.

Case 1.—B. F. M. (Med. No. 60102), 23 years old, white, single, a graduate of a teacher's college, was referred to one of us (S. A. L.) on July 24, 1941, with a diagnosis of patency of the ductus arteriosus, to be studied preparatory to ligation of the congenitally patent vessel.

Her chief complaint was partial loss of voice of three and one-half months' duration.

The family history was not contributory. The past history was not significant, except as will be noted in relation to the present illness.

Present Illness.—She stated that she was a blue baby at birth, but did not know how long this had persisted. Five years before entry, a physician had informed her that she had a cardiac murmur, but, to the patient's knowledge, no definite diagnosis was made. She had enjoyed good health except that physical activity had been moderately restricted because of fatigability and moderate dyspnea brought on by exertion. On occasions in the past, after a day of unusual activity, such as engaging in girls' sports, she had found that one week of rest was required to regain her usual feeling of well-being. There has been no further cyanosis as far as she knew, except that, when in swimming, there was some blueness about the nose and mouth. However, in spite of the dyspnea, she had been able to carry the full course of a student school teacher, including minor school gymnastics.

Three and one-half months before entry, in order to be on time for an interview for a position as school teacher, she ran one block and then ran up two flights of stairs. Immediately after this exertion, she found, to her utter embarrassment, that she was unable to speak. This was not complete aphonia, but inability to speak audibly. During the next two months her voice slowly returned, but had not yet regained its normal

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quality. This was most noticeable to the patient on raising her voice to speak to persons at a distance; the voice at these times lost its normal resonance and inflection, and occasionally became very gruff. Two weeks before entry she had consulted her private physician because of the impairment of her voice and decreased exercise tolerance. A diagnosis of patency of the ductus arteriosus was made, and the patient was referred to us for study preparatory to surgical obliteration of the abnormal vessel.

Pain of cardiac origin, orthopnea, and dependent edema had never been present. There was no history of rheumatic fever, growing pains, chorea, or frequent sore throats.

Physical Examination.—The patient was well developed and well nourished. She was able to lie flat in bed without any discomfort whatsoever. There was no cyanosis or clubbing of the fingers or toes. The voice seemed to be normal, but the patient stated that it did not have its usual quality. The head and neck were normal. The thyroid gland, although palpable, was not enlarged. There were no abnormal pulsations or thrills in the cervical vessels. The chest was negative to percussion and auscultation. The heart was slightly enlarged. The rhythm was normal, and the rate was 96. A prominent systolic pulsation was both visible and palpable on the anterior superior aspect of the left side of the chest, most marked in the second intercostal space immediately to the left of the sternal border, and a palpable shock corresponding to the pulmonic second sound was noted in the same location. The apical impulse was normal. There was a very soft (Grade I) apical systolic murmur, but no diastolic murmur was audible in this area. As the pulmonic area was approached, both heart sounds became markedly accentuated, especially the second sound. The abnormally loud sounds at the base suggested the presence of a systolic murmur, but the only murmur definitely audible in this area was a soft, early, blowing diastolic murmur, best heard in the second left intercostal space, but also heard to a less degree all along the left sternal border. The blood pressure readings were: right arm, 128/86; left arm, 100/78; left leg, 158/110; right leg, 170/104. After exercise, the blood pressure (right arm) rose to 186/90, with a corresponding rise in the pulse rate. During and after the exertion, she was moderately breathless, but there was no cyanosis or hoarseness.

Laboratory Data.—The blood Hinton and Wassermann reactions were negative. The urine was normal. Examination of the blood revealed a hemoglobin of 110 per cent (Sahli), an erythrocyte count of 5,700,000, a leucocyte count of 6,800, and a normal differential leucocyte count. The blood nonprotein nitrogen was 29 mg. per cent, and the cholesterol, 220 mg. per cent. The vital capacity was 3,200 c.c. The circulation time (dechlorin method) was 13 seconds, and the venous pressure, 120 mm. saline (right arm).

An electrocardiogram (Fig. 1) showed moderate right axis deviation and inverted T waves in Lead IV, but no other changes.

Fluoroscopic examination and roentgenograms of the heart (Fig. 2) showed definite cardiac enlargement, chiefly downward and to the left, with marked prominence of the pulmonary conus and marked dilatation of the intrapulmonary arteries. The right pulmonary artery measured 3 cm. in diameter, and showed marked systolic expansion. The aorta was indistinct and probably small, but was possibly obscured by the dilated pulmonary artery. There was only slight dilatation of the left

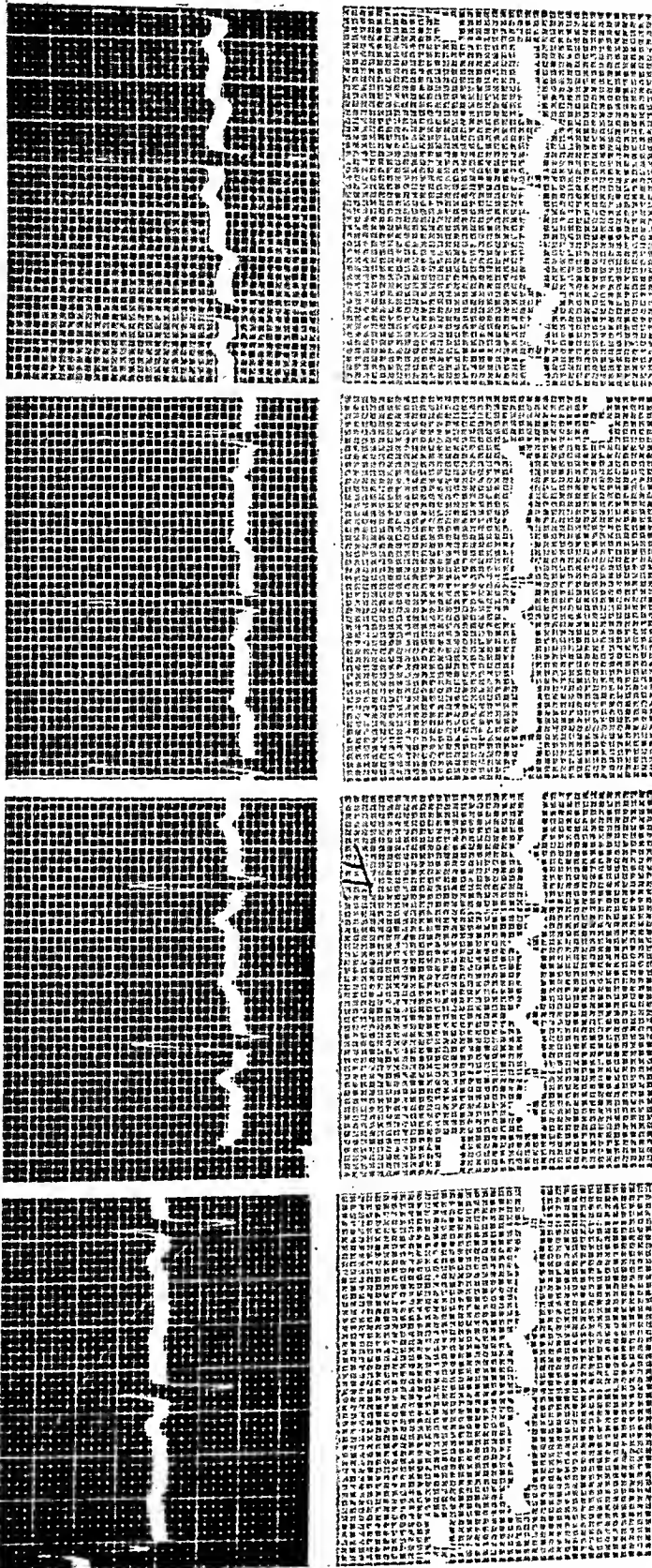


Fig. 1.—The upper tracings are from Case 1; they show well-marked right axis deviation, with normal form of the ventricular complexes, except that T_1 is inverted. The lower tracings, from Case 2, show well-marked right axis deviation, with normal form of the ventricular complex except that T_1 is inverted.

auricle posteriorly. The lungs, other than as mentioned above, were negative. No intracardiac calcification was seen. The measurements were as follows: Mr. 3.2, Ml. 10.8, G.V. 5.0, Int. Diam. 26.8.*

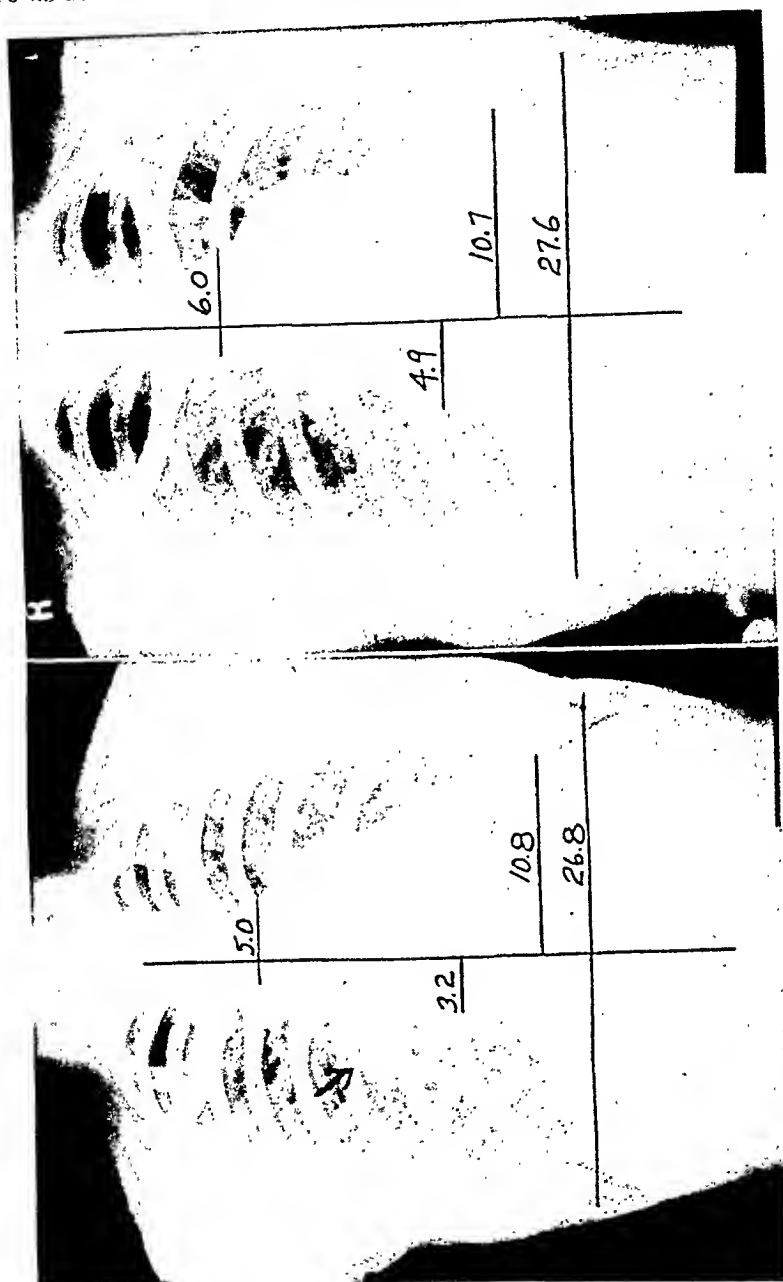


FIG. 2.—Roentgenograph on the left (Case 1) shows slight cardiac enlargement, a very prominent main pulmonary artery, and marked dilatation of the right pulmonary branch (arrow).

Roentgenograph on the right (Case 2) shows some general cardiac enlargement, a very prominent main pulmonary artery, and moderate enlargement of the pulmonary branches in the right hilum.

On laryngoscopic examination (by Dr. John R. Richardson) during rest, the left vocal cord was found to lie in the cadaveric position (Fig. 3). On phonation (Fig. 3), the right cord moved across the midline, but did not closely approximate the completely paralyzed left cord; this accounted for the abnormal quality of the voice. Furthermore, the left arytenoid cartilage showed no evidence of movement on phonation. It was the opinion of the examiner that, as time passed, the right cord would move sufficiently well to compensate for the lack of movement of

the left, thereby resulting in an almost complete return of the normal quality of the voice.

Case 2.—L. G. A. (Surg. No. 69113), 40 years old, single, white, a school teacher, was referred to Dr. F. C. Newton, of the surgical staff, on Oct. 7, 1941, for study because of the possibility of a mediastinal goiter.

Although the patient had many complaints, only those referable to the cardiovascular system concern us here. The family history was not contributory. The relevant past history is given with the present illness.

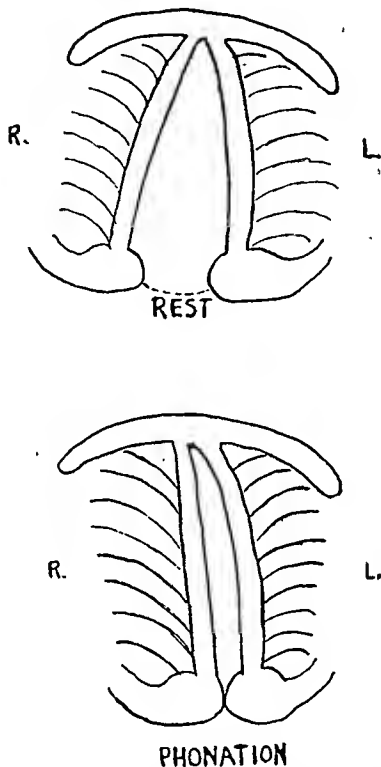


Fig. 3.—Drawing of the appearance of the vocal cords at rest (upper), and with phonation (lower). In both cases the appearance was essentially the same. Note immobility of the left vocal cord and compensatory movement of the right beyond the midline on phonation.

Present Illness.—She stated that she was a blue baby at birth, but did not know how long this had persisted. There was no history of rheumatic fever, growing pains, chorea, or frequent sore throats. Low-grade hoarseness, associated with a hissing sound on normal respiration, had been present since birth. Eleven years before entry, a laryngoscopic examination had been performed in connection with an operation on the nasal septum. She was told that the left vocal cord was paralyzed, and probably had been all her life. The hoarseness had never produced any disability, although it was more pronounced during fatigue and during upper respiratory infections.

Since childhood she had noticed that she was unable to exercise as much as other people because of fatigability and dyspnea. Climbing two flights of stairs produced temporarily incapacitating dyspnea. Mild palpitation had been present constantly, and became more severe on exertion or when she was fatigued. There was no history of cyanosis since birth. Neither orthopnea nor edema of the ankles had ever been present. There had been no pain of cardiac origin.

Physical Examination.—The patient was well developed, slightly obese, and did not appear ill. The temperature and pulse rate were normal. There was very slight cyanosis of the lips and fingernail beds. There was no clubbing of the fingers and toes. There was a small perforation of the nasal septum as a result of her previous operation. The remainder of the head and neck was normal. The thyroid gland was palpable, but was not enlarged or nodular. There were no abnormal pulsations of the cervical vessels. The lungs were normal to percussion and auscultation.

Percussion of the heart showed that the right border of dullness was parasternal, and that the left border of dullness was 7 cm. from the mid-sternal line (midclavicular line, 7.5 cm.). The rhythm was normal. The pulmonic second sound was markedly accentuated, and there was a long, low-pitched, blowing, diastolic murmur along the left sternal border, most marked in the second left intercostal space. No other murmurs were audible. The blood pressure was 140/90. The remainder of the physical examination was not contributory.

Laboratory Data.—The blood Hinton and Wassermann reactions were negative. The hemoglobin was 100 per cent (Sahli), the erythrocytes numbered 5,500,000, the leucocyte count was 7,600, and the differential leucocyte count was normal. The blood cholesterol was 206 mg. per cent. The vital capacity was 2,900 c.c. An electrocardiogram (Fig. 1) showed right axis deviation and inverted T waves in the fourth lead.

Fluoroscopic examination and posteroanterior and oblique roentgenograms of the heart (Fig. 2) showed definite cardiac enlargement, chiefly of the left ventricle. There was marked prominence of the pulmonary artery, which projected well beyond the heart border just below the arch of the aorta. This area showed expansion with systole which was more marked than normal. The intrapulmonary branches were slightly enlarged on the right, but showed no expansile pulsation. The lungs elsewhere were normal. There was no demonstrable dilatation of the left auricle, nor any intracardiac calcification. The measurements were as follows: Mr. 4.9, Ml. 10.7, G.V. 6.0, Int. Diam. 27.6

On laryngoscopic examination (by Dr. Lyman G. Richardson), the vocal cords during the resting state were found to be in the same position as those of the first patient (Fig. 3). However, on phonation, in contrast to the first case, the right cord moved far enough across the midline to compensate for the lack of movement of the paralyzed left cord, thereby resulting in a relatively normal quality of the voice.

COMMENT

The fact that both patients were following the same profession and that both were seen within four months of each other is a peculiar coincidence. Probably the most important clinical feature, however, is that both patients were referred to the hospital with the possibility in mind of surgical intervention, one for patency of the ductus arteriosus and the other for a substernal goiter. Now that surgical obliteration of a patent ductus arteriosus is possible, it is extremely important that every effort be made to arrive at the correct diagnosis in cases of congenital heart disease. This will avoid useless operation, which carries a mortality of 5 to 10 per cent.

The most unusual feature of these two cases was complete paralysis of the left vocal cord, apparently because of functional interruption of the recurrent laryngeal nerve where it loops around the aorta on its course to the neck. Hoarseness is a common complication of aneurysms of the arch of the aorta, and, as might be suspected, it also occurs with aneurysms of the pulmonary artery, the great majority of which are also caused by syphilis.³⁻⁵

Wahl and Gard⁵ presented one case of recurrent laryngeal nerve palsy produced by an aneurysm of the pulmonary artery in a patient with uncomplicated atrial septal defect. A similar case, but with dilatation rather than aneurysm of the pulmonary artery, was reported by Hotz (Case 2).⁶ E. Weiss' patient with Lutembacher's syndrome complicated by hoarseness was reported by Abbott.⁷ In Bedford, Papp, and Parkinson's Case 3² there was transient hoarseness after exertion. That hoarseness does not occur more frequently in congenital heart disease with left-right shunts, which may more than triple pulmonary flow, is rather surprising when one considers the anatomic relationship between the arch of the aorta, the pulmonary artery, and the recurrent laryngeal nerve. As a matter of fact, cases of Eisenmenger's syndrome complicated by recurrent nerve palsy have been reported by Baumgartner and Abbott⁸ and by Talley and Fowler.⁹ Furthermore, it is to be expected that any congenital cardiac defect that is associated with marked enlargement of the pulmonary artery may be complicated by left vocal cord paralysis.

Fetterolf and Norris,¹⁰ by their careful anatomic dissections, showed that hoarseness in cases of mitral stenosis is caused by compression of the recurrent laryngeal nerve between the dilated pulmonary artery (or the left pulmonary artery) and the inferior surface of the arch of the aorta where the nerve loops around the latter vessel on its way to the neck. From their description, it seems clear that hoarseness may be produced by this mechanism, regardless of the cause of the dilatation of the pulmonary artery. From the history, physical examination, and roentgenologic changes in the cases presented here, one is led to the conclusion that the recurrent nerve paralysis was produced by compression of the nerve between the aorta and the dilated pulmonary artery or one of its branches.

SUMMARY

Two cases of atrial septal defect with the unusual complication of recurrent laryngeal nerve paralysis are presented. The necessity of exact diagnosis of congenital heart disease is stressed because both patients were erroneously suspected of having diseases which are amenable to surgical treatment, namely, patency of the ductus arteriosus in one instance, and substernal goiter in the other.

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THE BASAL METABOLIC RATE IN ESSENTIAL HYPERTENSION

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THE literature relative to the effect of high blood pressure on basal metabolism is confusing because in some instances the authors failed to state the nature of the cases studied, and because, in other instances, patients had complications, such as myocardial failure of varying degrees, Cheyne-Stokes respiration, nephritis, ovarian failure, or possibly hyperthyroidism.¹⁻⁶ However, there is evidence that hypertension can increase the basal metabolic rate, but does not always do so.⁷⁻¹⁵

Of these reports, those of Keith and associates,¹³ Hayasaka,¹¹ Weiss,¹⁴ Weiss and Ellis,¹⁵ Becker,⁷ Boothby and Sandiford,⁸ and Crile and McCullagh⁹ are most pertinent to our presentation, which deals with the effect of uncomplicated high blood pressure on the basal metabolic rate. Keith and associates measured the basal metabolic rate in thirty-nine cases of malignant (Group 4) hypertension; in eight instances the basal rate was greater than plus 20 per cent.¹³ Although these authors could not explain their observations, they expressed the belief that the thyroid gland was not responsible. Hayasaka obtained an average basal metabolic rate of minus 6 per cent in a group of cases of "benign" hypertension, and an average of plus 18 per cent in a group of "malignant" hypertension. He found that neither the pulse rate nor the diastolic blood pressure was directly related to the basal metabolism. Weiss and Ellis obtained basal metabolic rates varying from plus 15 to plus 50 per cent in seven of eleven patients who had hypertension with normal cardiac function.¹⁵ Although they admitted that the cause for this elevation of the basal rate was unknown, they expressed the belief that an active sympathetic nervous system must be present. One patient of these authors had a basal metabolic rate of plus 45 per cent, associated with a blood pressure of 270/140. Thyroideectomy caused reduction of the rate to normal, but did not influence the blood pressure. In a study of sixteen patients who had essential hypertension and no cardiac failure, Becker noted basal rates varying from plus 17 to plus 38 per cent. He concluded that this phenomenon was due to a thyrogenic component, as he obtained a return of the basal metabolic rate to normal after roentgen treatment of the thyroid gland. The blood pressure decreased in some cases.

On the other hand, Boothby and Sandiford,⁸ in a statistical study of 170 patients who had high blood pressure, found that approximately 90 per cent of them had basal metabolic rates within the range of plus 15

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to minus 15 per cent. Crile and McCullagh⁹ discussed means of distinguishing an elevated basal metabolic rate in the presence of hypertension from that due to hyperthyroidism. They suggested that the increased basal rate in many cases of hypertension might be the result of the increased cardiovascular activity required to maintain the circulation against a high diastolic blood pressure. Mosler and Edelstein¹⁶ found a normal metabolic rate in "pure" forms of essential hypertension. Kusakabe and Ito¹⁷ found a normal rate in five cases of essential hypertension. The literature is, therefore, conflicting with respect to the basal metabolic rate in uncomplicated essential hypertension. The opinions range from observations that there is almost uniform elevation of the basal metabolic rate to those which indicate that the rate is normal in hypertension. Additional studies relative to the basal metabolism in hypertension may be found in articles by Boas and Shapiro,^{18, 19} Fishberg,¹⁰ Hamilton and Knight,²⁰ Mannaberg,²¹ and Rose.²²

Our method of approach to this problem was a study of case records from the files of the Mayo Clinic. Only records of patients who had essential hypertension and whose basal metabolic rates had been measured were used. From this group were discarded: (1) all cases in which clinically there was even questionable cardiac decompensation; (2) all cases in which there was definite or probable hyperthyroidism, in the judgment of the consultant who examined the patient; and (3) all cases of secondary hypertension due to, or associated with, severe renal disease, adrenal tumors, or pituitary basophilism. The final group consisted of 827 cases, the analysis of which constitutes the basis for our study. They were classified according to the method of Keith, Wagener, and Barker.²³ Group 1 included those patients who had only a mild narrowing or sclerosis of the retinal arterioles. Patients in Group 2 usually had moderate to marked sclerosis of the retinal arterioles, either of the chronic type characterized by exaggeration of the arterial reflex and arteriovenous compression, or of the postangiospastic type characterized by generalized and localized irregular narrowing of the arterioles. Patients who had hypertension, Group 3, had retinitis of the angiospastic type characterized by edema, cotton-wool patches, and hemorrhages in the retina, in combination with sclerotic and spastic lesions in the arterioles. Patients in Group 4 had edema of the nerve heads of the retinas, in addition to the retinal changes characteristic of hypertension, Group 3.

Two measurements of blood pressure were made in each case with a standard mercury sphygmomanometer. One was made during the clinical examination,* and one at the time of measurement of the basal metabolic rate.† All the patients had a systolic blood pressure of 150 mm. of mercury, or more, at the time of the clinical examination. The basal metabolic rates were measured by the technique outlined by

*Hereinafter referred to as clinical blood pressure.

†Hereinafter referred to as basal blood pressure.

TABLE I

DISTRIBUTION OF PATIENTS BY GROUP OF HYPERTENSION, SEX, AND AVERAGE AGE

GROUP	TOTAL	MALES	FEMALES
1	204	51 (38)*	153 (48)
2	437	109 (48)	328 (48)
3	146	60 (46)	86 (48)
4	40	19 (44)	21 (45)
Total	827	239	588

*The figures in parentheses indicate average age in years.

TABLE II

AVERAGE BLOOD PRESSURE IN EACH OF FOUR GROUPS OF HYPERTENSION

GROUP	BLOOD PRESSURE, MILLIMETERS OF MERCURY			
	CLINICAL*		BASAL†	
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
1	172	102	150	90
2	208	124	174	106
3	225	140	191	120
4	243	156	212	139
Average	204	123	173	106

*Indicates blood pressure in the clinic.

†Indicates pressure at time that basal metabolic rate was measured.

TABLE III

AVERAGE BASAL METABOLIC RATE BY GROUP OF HYPERTENSION AND SEX OF PATIENTS

GROUP	AVERAGE BASAL METABOLIC RATE, PER CENT		
	TOTAL	MALES	FEMALES
1	+ 3	+4	+ 3
2	- 4	+4	+ 4
3	+ 5	+4	+ 6
4	+11	+8	+13
Average	+ 4	+4	+ 4

Boothby and Sandiford.^{8, 24} Part of the clinical data are presented in Tables I and II. They do not require any comment.

The relationship of the basal metabolic rate to the hypertension in each group is shown in Table III and Fig. 1. The average metabolic rates in Groups 1 and 2 were essentially the same. The average rate of metabolism in Group 3 was slightly greater than that in Groups 1 and 2. The average rate of metabolism in Group 4 was about twice as much above normal as the average of Group 3 was above the normal. Considerable variability of metabolism was present in each group. Of the 204 patients in Group 1, fourteen had rates greater than plus 15 per cent (7 per cent), and, of these, two were greater than plus 20 per cent. In Group 2, thirty of the 437 patients had rates greater than plus 15 per cent (7 per cent), and, of this number, nine were greater than plus 20 per cent. In Group 3, seventeen of the 146 patients had rates greater than plus 15 per cent (12 per cent), and eight were greater than plus 20 per cent. Of the forty patients in Group 4, eleven had basal metabol-

ic rates in excess of plus 15 per cent (27 per cent), and four had rates greater than plus 20 per cent (Table IV). When the average basal metabolic rates of patients classified according to their basal systolic blood pressure are charted, there is shown to be a relationship (Fig. 2);

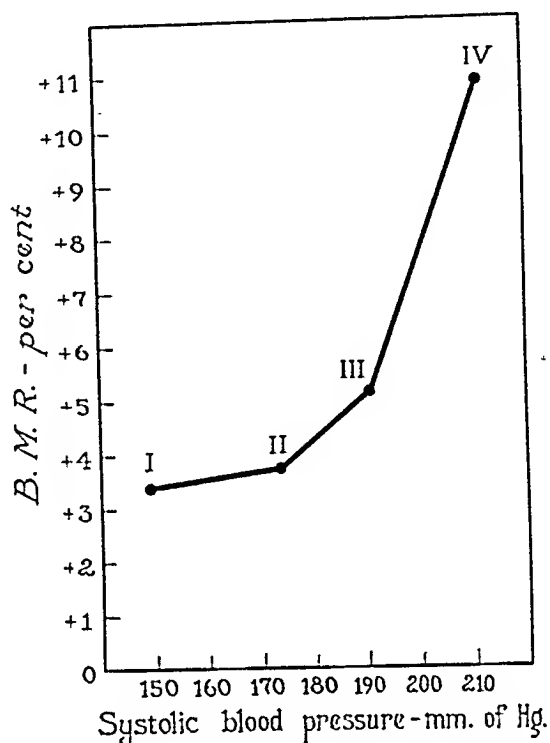


Fig. 1.—Average basal metabolic rates and basal systolic blood pressures of patients in each of four groups of hypertension.

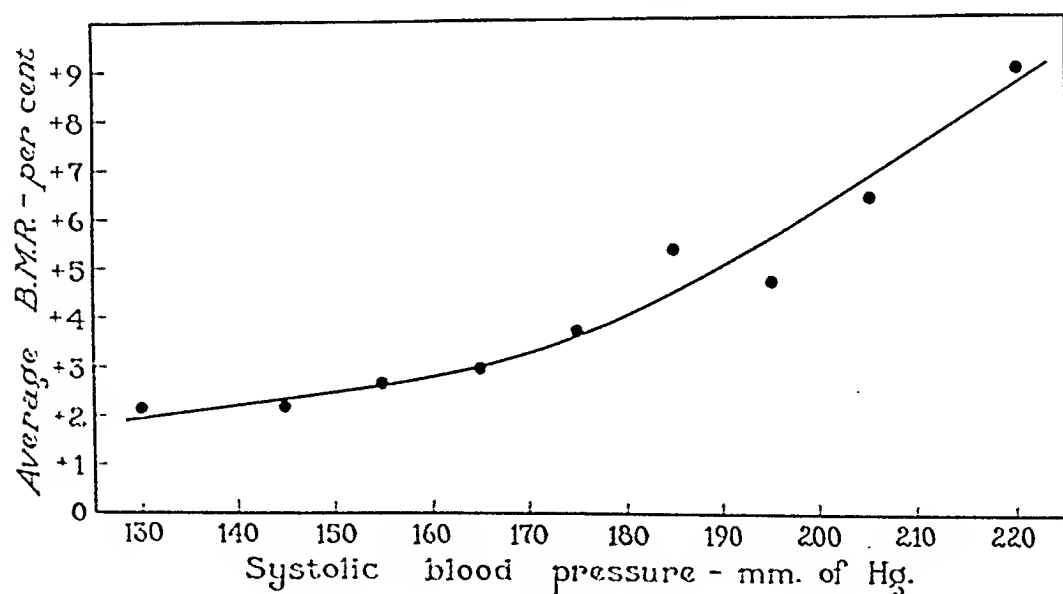


Fig. 2.—Average basal metabolic rates of patients classified according to their basal systolic blood pressures.

however, when individual cases are considered, there is shown to be very little correlation between basal metabolism and blood pressure (correlation coefficient = plus 0.2).

TABLE IV

PERCENTAGE DISTRIBUTION OF CASES IN EACH OF FOUR GROUPS OF HYPERTENSION ACCORDING TO BASAL METABOLIC RATE

BASAL METABOLIC RATE	PERCENTAGE OF CASES			
	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Less than -15%	2	2	1	
-15% to +15%	91	91	87	73
Greater than +15%	7	7	12	27
Total	100	100	100	100

Most hypotheses relative to the elevated basal metabolism in essential hypertension involve the thyroid gland or the cardiac or respiratory systems. The basal metabolism tends to rise with the increased respiration associated with cardiac decompensation.^{5, 25} Our patients were, however, as far as could be ascertained, free of dyspnea. Heart rate may, perhaps, influence the metabolism. Lev and Hamburger²⁶ studied a patient who could produce paroxysmal tachycardia at will, and found the basal metabolic rate to be minus 6 per cent with a pulse rate of 67, and plus 5 per cent when the pulse rose to 187. Our patients had essentially normal heart rates.

Some students of the subject have believed that the increased cardiac work resulting from the increased blood pressure might be the reason for increased metabolism in some cases of hypertension. Our data would seem to lend some support to this conclusion, for the average basal metabolic rate of all patients who had hypertension, Group 4, was higher than the average basal metabolic rate of all patients who had hypertension, Group 3, and these, in turn, had a higher average basal metabolic rate than patients who had hypertension, Group 2. We have shown that the average blood pressure of patients increases in each succeeding group (Table II). Thus, through hypertension Groups 1, 2, 3, and 4, there are a gradually increasing average blood pressure and gradually increasing average basal metabolic rate.

As indicated earlier, however, the correlation in individual cases is small. Further study of our cases is shown in Table V. Only patients who had a basal diastolic blood pressure of 130 mm. of mercury, or more, were included in Table V, for it was felt that hearts which were maintaining such high blood pressures were certainly overworking. In Group 3, only a fifth of the patients had a basal metabolic rate greater than plus 15 per cent, and, in Group 4, only about a third of the patients had basal metabolic rates exceeding plus 15 per cent. In other words, four-fifths of patients who have hypertension, Group 3, and diastolic blood pressures exceeding 130 mm. have metabolic rates which are within the accepted range of normal. Similarly, two-thirds of pa-

tients who have hypertension, Group 4, and diastolic blood pressures exceeding 130 mm. have basal metabolic rates within the accepted range of normal. If an increase of cardiac work had a marked effect on basal metabolic rate, probably more patients who have severe hypertension should have metabolic rates greater than normal. This evidence, we feel, shows the lack of marked relationship between an increased basal metabolic rate and cardiac work, per se.

TABLE V

DISTRIBUTION OF ALL CASES IN WHICH THE BASAL DIASTOLIC BLOOD PRESSURE WAS 130 MM. OR MORE, ACCORDING TO BASAL METABOLIC RATE

BASAL METABOLIC RATE	HYPERTENSION GROUP 3 (43 CASES)			HYPERTENSION GROUP 4 (25 CASES)		
	CASES	AVERAGE BASAL METABOLIC RATE	AVERAGE BASAL DIASTOLIC BLOOD PRESSURE	CASES	AVERAGE BASAL METABOLIC RATE	AVERAGE BASAL DIASTOLIC BLOOD PRESSURE
More than +15	8	+22	144	8	+22	147
0% to +15%	26	+ 8	135	16	+10	153
Less than 0%	9	- 5	130	1	- 7	130

In order to ascertain whether or not hypertension might provoke hyperthyroidism, microscopic sections of the thyroid glands of forty additional patients who had died of congestive heart failure due to hypertension were examined microscopically. In the forty cases studied there were none of the usual morphologic changes which are associated with hyperthyroidism. Kyser²⁷ was unable to find any more evidence of hyperthyroidism in thyroid sections of patients who had died of high blood pressure than in a control group. This is in accord with the results of others (Rose). Resnik and Friedman²⁸ have shown that congestion of the thyroid gland does not have any effect on the basal metabolism, as had been suggested by Lev and Hamburger.

We have noted a few instances in which partial thyroidectomy was done on patients who had severe hypertension and showed evidence of coexistent hyperthyroidism, but in whose thyroid glands no evidence of parenchymatous hypertrophy could be found. The elevated basal metabolic rate has not fallen appreciably after double resection of the thyroid glands in these cases. The increased metabolism was therefore linked with the hypertension.

In a recently examined series of sixty-nine patients who had essential hypertension and hyperthyroidism, in twenty-one cases the basal metabolic rate failed to fall as low as plus 20 per cent within two weeks of partial thyroidectomy, presumably because of hypertension. It is of interest that the average blood pressure readings both before operation and after operation were higher in these twenty-one cases than in the others. We have seen a number of patients who had hypertension and frank hyperthyroidism, in whom, after partial thyroidectomy with com-

plete relief of all clinical manifestations of hyperthyroidism, the basal metabolic rate has remained at levels greater than plus 20 per cent for years. In many of these patients the thyroid tissue which was removed showed the typical pathologic picture of exophthalmic goiter, but repeated periods of administration of iodine after the operation failed to lower the basal metabolic rate or alter the patient's clinical condition. This situation also seems to be due to hypertension.

We have observed a few instances of high-grade myxedema with associated severe hypertension in which repeated basal metabolic rates failed to be as low as minus 20 per cent. In three such cases that have come to our attention, administration of desiccated thyroid in quantities only sufficient to control the clinical evidence of myxedema has raised the basal metabolic rate to more than zero. It would seem likely, therefore, that the elevation of the basal metabolic rate in some cases of hypertension is probably independent of the thyroid gland or of excess thyroxin in the body tissues. The frequently repeated observation that elevated basal metabolic rates in many cases of hypertension will fall to normal levels after a few days' rest in bed also suggests that thyroxin is not present in excessive amounts.

It would seem logical to assume that the basal metabolic rate is elevated in some cases of hypertension because of inability of the patients to relax sufficiently to allow the test to be made under true basal conditions. It is admitted, however, that this explanation does not account for the failure of elevation of the basal metabolic rate in many other hypertensive patients who appear equally tense, nor do we feel that there is evidence to indicate that such a condition is necessarily the only factor tending to cause increased basal metabolic rates in some cases of hypertension. To our knowledge, no adequate explanation for this occurrence seems to be available. For the time being we can make no further observation than that hypertension and elevated basal metabolic rate are frequently associated in the absence of hyperthyroidism. The difficulty of differential diagnosis between hypertension with and without true primary hyperthyroidism makes further investigation of these patients important.

SUMMARY

A study of 827 cases of hypertension, in which thyroid disease was excluded as accurately as possible by clinical methods, showed that the basal metabolic rates were elevated, to higher levels and more frequently, in patients with higher blood pressures than in those with less marked hypertension. No adequate explanation of this phenomenon is apparent, although in our opinion the thyroid gland itself is not responsible.

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THE RELATIVE CLINICAL POTENCY OF DIGITALIS U.S.P. X, DIGITALIS U.S.P. XI, AND DIGILANID

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DIGITALIS therapy is based largely on the presumption that the various preparations in use are of known relative potency. Much difficulty has arisen, therefore, from the fact that the digitalis of U.S.P. XI (1936) is substantially more potent than that of U.S.P. X (1926), and that the precise difference in potency is still uncertain. The increase in strength of the official preparation of digitalis resulted from a change of the standard to which the drug is compared. Prior to 1936, digitalis was assayed in terms of ouabain. Since that time it has been made to conform in potency to the international standard powder adopted by the Health Committee of the League of Nations in 1925. The strength of the standard digitalis powder is such that 89.7 milligrams is the lethal dose per kilogram of cat. The "international digitalis unit" consists of 0.1 Gm. of the powder, and is the equivalent of 1.1 cat unit.

Judging from bio-assay by the frog and cat methods, the digitalis of U.S.P. XI appears to be from 25 per cent to 30 per cent stronger than that of U.S.P. X.¹ Clinical experience, however, has not yet demonstrated to what extent these figures are applicable to the therapeutic potency of digitalis. Bland and White² "suspect that in actual practice, an increase in potency up to 50 per cent is more nearly correct." Under the circumstances, it is desirable that the action of the newer preparation of digitalis should be carefully compared with that of the preparation previously in use in order to establish an accurate basis for modification of the prescribed clinical dosage. It is also of value to ascertain more precisely the relative strength of digilanid, a form of digitalis which has attracted recent attention because of the fact that it can be assayed chemically, thus assuring consistent potency. Digilanid is composed of the chemically pure glycosides of *Digitalis lanata*.

The following study presents a clinical evaluation of the potency of digitalis U.S.P. X, digitalis U.S.P. XI, and digilanid, in terms of the ability of these drugs to slow the ventricular rate in cases of auricular fibrillation. As will later be discussed, this action of digitalis is not identical with that by which the efficiency of ventricular contraction is improved or "toxic" effects are elicited. Conclusions as to digitalis potency which are based upon slowing of the ventricular rate in the presence of auricular fibrillation should not be compared without qualification to the results of assay by techniques which involve other functions of the drug.

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METHODS

Observations were made on a series of seventeen patients who had chronic auricular fibrillation and were under treatment in the Cardiac Clinic of the Philadelphia General Hospital. All patients were ambulatory. Their ages ranged from 32 to 69 years. Evidence of organic heart disease of rheumatic, hypertensive, or arteriosclerotic origin was present in all cases. The observations to be reported were made in the course of routine clinic visits at intervals of one to six weeks.

The routine consisted of digitalizing each patient with one of the three preparations studied, and thereafter giving a constant daily dose which was the same for all patients, irrespective of individual therapeutic indications. The daily dose of digitalis U.S.P. X (Upjohn) was $1\frac{1}{2}$ grains (0.1 Gm.), of digitalis U.S.P. XI (Squibb), 1 grain (0.065 Gm.), and of digilanid (Sandoz), $\frac{1}{200}$ grain (0.3 mg.). When the ventricular rate had become stabilized, the studies described below were carried out. After the completion of study of each preparation, one of the others was substituted and the procedure repeated.

The criterion of potency of the drugs was the rate of contraction of the ventricles after a control period of rest in the seated posture and after exercise. The rate was counted first for one minute by auscultation. The patient then walked ten times over a two-step staircase, each step of which was 8 inches high. The patient selected his own pace, but was made to maintain it consistently in all subsequent tests. As the patient returned to his seat, the stethoscope was applied to his chest and the ventricular rate counted continuously from the moment he sat down until three minutes later; notation was made of the number of beats in each fifteen-second interval. A record was kept also of the room temperature and the patient's blood pressure, weight, and general condition, in order to eliminate factors which might render successive tests not comparable.

Electrocardiograms were recorded continuously before, during, and after exercise in several cases. From these it was apparent that the ventricular rate during the first fifteen seconds after exercise was the same as the maximum rate during exercise. Therefore, for the purposes of the present study, the rate during the first fifteen seconds of rest has been called the "maximum exercise rate."

The rate of the ventricles was the only objective criterion used in comparing the action of the three drugs. No account was taken of a pulse deficit, for estimates of this phenomenon are usually inaccurate, and are essentially an index of the tactile appreciation of the observer, rather than of any significant abnormality of circulatory function.

RESULTS

Comparison of digitalis U.S.P. X and digitalis U.S.P. XI was made in ten cases, of digitalis U.S.P. X and digilanid in sixteen cases, and of digitalis U.S.P. XI and digilanid in eleven cases. Table I summarizes the results obtained in ten cases in which all three preparations were compared on each patient. Because of differences between individual patients in their reaction to digitalis, only the cases included in Table I could be used as the basis for the following discussion. Confirmatory evidence, however, was afforded by the results obtained in the seven remaining cases, in which the effects of only two preparations were compared on each patient.

TABLE I

VENTRICULAR RATES IN TEN CASES OF AURICULAR FIBRILLATION, SHOWING THE RELATIVE EFFECT OF DAILY DOSES OF $\frac{1}{3}$ MG. OF DIGILANID, $1\frac{1}{2}$ GRAINS OF DIGITALIS U.S.P. X, AND 1 GRAIN OF DIGITALIS U.S.P. XI

(The rates were counted when the patient was seated [1] after rest, [2] during the first fifteen seconds after exercise, [3] during the first minute after exercise, and [4] during the second minute after exercise.)

PATIENT		DIGILANID				DIGITALIS U.S.P. XI				DIGITALIS U.S.P. X			
AGE (YEARS)	ETIOLOGIC TYPES OF HEART DISEASE	REST	EXERCISE	1ST MIN.	2ND MIN.	REST	EXERCISE	1ST MIN.	2ND MIN.	REST	EXERCISE	1ST MIN.	2ND MIN.
1. 34	Rheumatic	83 92	136 172	118 143	88 98	78 75	128 132	112 109	87 83	72 62	128 124	97 96	74 68
	Average	88	154	131	93	77	130	111	85	69	128	102	74
2. 34	Rheumatic	54 60 49 59	132 124 120 116	108 97 93 100	66 61 57 58	72 48 60	128 112 108	104 82 95	72 48 65	49 50 44	116 124 96	90 90 77	67 52 54
	Average	56	123	99	61	60	116	94	62	48	112	86	58
3. 38	Rheumatic	68 67	144 112	118 89	78 67	57 61	132 120	100 92	62 62	60 71 57	120 140 132	89 102 104	60 74 57
	Average	68	128	104	73	59	126	93	62	63	131	98	64
4. 51	Rheumatic	92 93	136 140	120 121	102 93	77 84 80	124 120 140	105 107 107	79 87 82	80 75	124 132	104 112	87 86
	Average	93	138	121	98	80	121	106	83	78	128	108	87
5. 50	Hypertension	75 79	140 144	121 115	89 87	86 83	112 108	98 96	87 85	75 74 74	124 112 120	104 99 106	83 83 84
	Average	77	142	118	88	85	110	97	86	74	119	103	83
6. 50	Hypertension	60 62 77 66	72 80 88 80	70 74 85 76	61 65 78 68	77 82 79	92 100 96	81 87 84	81 84 83	61 64 74 66	76 80 88 81	70 75 86 77	67 66 82 72
	Average	66	80	76	68	79	96	84	83	66	81	77	72
7. 58	Hypertension	72 72 81	124 116 132	102 106 115	74 82 83	79 94	112 124	100 120	87 106	88 75	132 116	119 103	93 83
	Average	75	124	108	80	87	118	110	97	82	124	111	88
8. 69	Arteriosclerosis	83 88 71 81	136 128 104 123	111 121 95 110	93 88 80 87	81 78 81 80	108 116 103 113	98 101 81 101	84 82 81 82	85 79 80 81	124 128 124 125	107 110 107 108	90 80 83 84
	Average	81	123	110	87	80	113	101	82	81	125	108	84
9. 54	Arteriosclerosis	69 45 54 56	124 84 104 104	95 76 84 85	78 50 63 64	72 45 52 56	136 116 104 119	99 85 86 90	81 59 75 72	65 60	100 120	87 92	69 69
	Average	56	104	85	64	56	119	90	72	63	110	90	69
10. 64	Arteriosclerosis	78 73 67 73	120 100 96 105	104 91 91 95	86 83 76 82	80 71 80 77	112 116 112 113	102 98 103 101	83 76 85 81	68 70	104 100	95 90	80 76
	Average	73	105	95	82	77	113	101	81	69	102	93	78
Average of all patients		73	122	105	79	74	116	99	79	69	116	98	76

It is apparent from Table I that the same dose of digitalis does not necessarily produce the same ventricular rate in different patients. Thus, $\frac{1}{200}$ grain (0.3 mg.) of digilanid per day produced a ventricular rate at rest of 45 per minute in one patient and 93 per minute in another, and ventricular rates during exercise which varied from 72 to 172 per minute between different patients. This, of course, simply emphasizes the clinical experience that the optimum daily dose of digitalis, irrespective of its form or consistent potency, is not the same for all patients.

Comparing the two preparations of *Digitalis purpurea*, U.S.P. X, $1\frac{1}{2}$ grains (0.1 Gm.), and U.S.P. XI, 1 grain (0.06 Gm.), Table I shows that the average ventricular rates which they produced were remarkably similar. The average ventricular rate at rest produced by digitalis U.S.P. X was slightly slower than that produced by digitalis U.S.P. XI, but during and after exercise the two were practically identical. As to individual cases, four patients had a slightly lower rate when digitalis U.S.P. X was used, four had a slightly lower rate when digitalis U.S.P. XI was used, and two had approximately the same rate with either preparation. These results indicate that 1 grain (0.06 Gm.) of digitalis U.S.P. XI has an effect equivalent to $1\frac{1}{2}$ grains (0.1 Gm.) of digitalis U.S.P. X. The potency of digitalis U.S.P. XI is therefore 50 per cent higher than that of digitalis U.S.P. X in terms of slowing action on the ventricular rate in the presence of auricular fibrillation.

Comparing digilanid with *Digitalis Purpurea*, Table I shows that the effect on the ventricular rate at rest was the same for $\frac{1}{200}$ grain (0.3 mg.) of digilanid as it was for $1\frac{1}{2}$ grains (0.1 Gm.) of digitalis U.S.P. X or 1 grain (0.06 Gm.) of digitalis U.S.P. XI. The ventricular rate during exercise, however, averaged six beats per minute higher when digilanid was used than during the administration of either preparation of *Digitalis purpurea*. Presumably therefore, $\frac{1}{200}$ grain (0.3 mg.) of digilanid is slightly less potent in controlling the rise in ventricular rate during exercise than is $1\frac{1}{2}$ grains (0.1 Gm.) of digitalis U.S.P. X or 1 grain (0.06 Gm.) of digitalis U.S.P. XI.

It is customary in practice to modify the dose of digitalis to some extent in accordance with the patient's personal evaluation of such symptoms as breathlessness, palpitation, rapid or slow heart action, or nausea. The seventeen patients of this series were therefore asked from time to time whether they preferred digitalis or digilanid, and their reasons for so doing. Three preferred digitalis because they regarded it as "stronger" than digilanid. Four preferred digilanid because it was "easier to take" or "less nauseating" than digitalis. The remaining ten patients had no preference or changed their opinion so often that no significance could be attached to it.

Conspicuous differences between the three preparations in their "toxic" effects upon the heart were not apparent. The incidence of

premature contractions, as far as this could be judged by auscultation, did not seem to be influenced by changing from one preparation to another. There was likewise no basis for any definite conclusion as to the relative ability of the drugs to improve myocardial efficiency. The occurrence of signs of congestive heart failure did not have any obvious relationship to which particular preparation was used as long as the routine dosage was unchanged.

DISCUSSION

The data which have been presented constitute a basis for the evaluation of digitalis potency only in terms of effect on the ventricular rate in the presence of auricular fibrillation. The technique of study which was employed was not adapted to the accurate estimation of either the "toxic" action of digitalis or its therapeutic action in improving the efficiency of myocardial contraction.³ Since the "toxic" effects may constitute an important factor in the bio-assay of digitalis by the frog or cat methods, it is easy to understand that estimates of digitalis by such standards may well differ from estimates based on the criterion of ventricular slowing. The same may be true also of the assay of digitalis in terms of its therapeutic effect in cases of normal sinus rhythm, when the drug action involves essentially the improvement of myocardial efficiency. The latter aspect of digitalis action is certainly the one most difficult to evaluate with accuracy, especially in cases of auricular fibrillation, in which ventricular acceleration plays an important role in the production of congestive phenomena. From the present study, the most that can be stated in regard to relative "toxic" effect (ectopic beats) or effect on the efficiency of myocardial contraction is that no conspicuous differences were observed between the results of a daily dose of $\frac{1}{200}$ grain (0.3 mg.) of digilanid, $1\frac{1}{2}$ grains (0.1 Gm.) of digitalis U.S.P. X, and 1 grain (0.06 Gm.) of digitalis U.S.P. XI.

The evidence which has been presented seems, on the other hand, to indicate with reasonable certainty that the relative potency of the three preparations in terms of slowing of the ventricular rate in the presence of auricular fibrillation is such that 1 grain (0.06 Gm.) of digitalis U.S.P. XI is exactly equal to $1\frac{1}{2}$ grains (0.1 Gm.) of digitalis U.S.P. X, and that the potency of $\frac{1}{2}$ grain (0.03 Gm.) of digilanid is slightly less than that of the other preparations. It is noteworthy that the difference in effectiveness of digilanid was apparent only during the exercise tolerance test. Judging from the ventricular rate when the patient was at rest, it might be assumed that no such difference existed. This fact illustrates a potential source of error when various forms of digitalis are compared and no account is taken of the rise in ventricular rate during exercise. It is evident from clinical experience that the resting ventricular rate in a case of auricular fibrillation is no indication whatever of the extent to which the rate increases during exercise.⁴

This acceleration of the rate during exercise is stated⁵ to be due in the average case to decreased vagal tone. Conceivably, therefore, the fact that digilanid produced the same ventricular rate at rest as did digitalis, but permitted a greater increase in rate during exercise, may imply that the difference in potency between these preparations may involve only their vagal action. This possible qualitative distinction, however, is not supported by sufficient evidence from the present study to warrant its acceptance without further investigation.

CONCLUSIONS

1. Daily oral doses of 1 grain (0.06 Gm.) of digitalis U.S.P. XI, $1\frac{1}{2}$ grains (0.1 Gm.) of digitalis U.S.P. X, and $\frac{1}{200}$ grain (0.3 mg.) of digilanid produced the same average ventricular rate at rest in cases of auricular fibrillation.

2. The degree of acceleration of the ventricular rate by exercise was the same when either of the two preparations of digitalis was given in the dosage stated above, but the degree of acceleration was slightly greater when digilanid was given.

3. Assayed in terms of their ability to slow the ventricular rate in cases of auricular fibrillation, 1 grain (0.06 Gm.) of digitalis U.S.P. XI is the equivalent of $1\frac{1}{2}$ grains (0.1 Gm.) of digitalis U.S.P. X. The potency of digitalis U.S.P. XI is therefore 50 per cent higher than that of digitalis U.S.P. X.

4. The potency of $\frac{1}{200}$ grain (0.3 mg.) of digilanid is slightly less than that of 1 grain (0.06 Gm.) of digitalis U.S.P. XI, or $1\frac{1}{2}$ grains (0.1 Gm.) of digitalis U.S.P. X.

5. Within the limited scope of this study, there was no evidence of any difference between the three preparations in either their "toxic" action or their influence on myocardial efficiency. It is emphasized, however, that the type of assay used is only accurate in evaluating the effect of digitalis on the ventricular rate in the presence of auricular fibrillation.

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Clinical Reports

RHEUMATIC THROMBOPHLEBITIS

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THE development of venous thrombosis in acute rheumatism has received various interpretations. Schmitt,¹ in 1884, expressed the view that thrombosis was the result of some alteration in the blood, rather than of an antecedent phlebitis. Gatay,² in 1895, described inflammatory changes in the vein wall and concluded that the thrombosis was entirely secondary to the associated phlebitis. Garnier³ and others, however, regarded venous stasis as the main factor, but conceded that changes in the blood and in the vein itself may be contributory.

Poynton⁴⁻⁶ reported extensive venous thrombosis in three children with rheumatic fever and subsequently observed ten additional cases of similar nature. In every instance there were manifestations of acute rheumatism at the time of thrombosis, a fact which the author considered presumptive evidence of active infection in the vein itself. Welch,⁷ in 1900, agreed that phlebitis is a definite but uncommon complication of acute rheumatism. He considered the former of minor significance, however, in the causation of venous thrombosis in heart disease. In a review of twenty-eight cases complicating cardiac diseases in general, Welch found only three in which there was a history of recent joint symptoms. Sladen and Winternitz,⁸ furthermore, have emphasized that any lesion of the heart resulting in congestive failure may be associated with venous thrombosis. In reviewing twenty-six rheumatic cases, they found that the interval between rheumatic fever and venous thrombosis varied from several months to many years; consequently, the authors were unable to establish that rheumatism was a definite etiological factor.

The histologic evidence that rheumatic foci occur within the venous system has likewise been inconclusive. In most instances, non-specific changes, in the nature of small round cell infiltrations and fibrosis of the vein wall, have been reported. Such alterations, obviously, may have been the result of venous thrombosis, rather than its cause. Perry,⁹ however, in a case of acute rheumatic fever complicated by thrombosis of the right innominate vein, demonstrated, for the first time, lesions closely resembling Aschoff nodules in the media of the vein.

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The purpose of this paper is to record the second case of rheumatic thrombophlebitis in which the diagnosis was confirmed by histologic studies. It differs from the case of Perry in that other clinical and pathologic manifestations of acute rheumatism were absent, and, therefore, is unique.

CASE REPORT

J. S., a 39-year-old white Italian, a printer by occupation, was admitted to the hospital June 4, 1941, with the complaint of pain and swelling on the left side of the neck, shortness of breath on exertion, and swelling of the ankles. He had had typhoid fever, diphtheria, scarlet fever, and recurrent tonsillitis in childhood. In 1928 he suffered from painful joints, and, in 1937, had had a severe attack of influenza. In 1938 a diagnosis of mitral stenosis was made at this hospital when the patient was admitted for an unrelated cause. Shortness of breath on exertion had occurred intermittently since 1933, and, for two months prior to the present admission, dyspnea was marked even on walking a short distance on level ground. Swelling of the legs had been noted intermittently for a period of one month. On June 2, 1941, the patient experienced severe pain on the left side of the neck, followed, the next day, by swelling of the tissues in that area. He also complained of sharp pain on both sides of the chest on breathing, and of a cough productive of bloody sputum.

On physical examination, the patient appeared orthopneic, cyanotic, and toxic. His temperature was 100.4° F. The sclerae showed moderate icterus. There were tenderness and induration of the deep cervical nodes at the angle of the jaw on the left. Tender lymph nodes were palpated in the left supraclavicular region and in the left axilla. There were fullness and induration over the anterior triangle of the neck and in the supraclavicular and infraclavicular fossae on the left side. The breath sounds were diminished over the left infraclavicular region, and over both bases posteriorly there was dullness to flatness on percussion, with diminished to absent voice and fremitus, and many small moist râles on inspiration. The left border of the heart was 1½ cm. outside the left midclavicular line. The heart rate was 120 per minute, and the beat was regular except for occasional ectopic systoles. The blood pressure was 118/78. There was a mid-diastolic thrill over the apex. The heart sounds were fairly well transmitted, and there was a snapping first sound at the mitral area, with an accentuated pulmonic second sound. There was gallop rhythm at the tricuspid area, and a diaphasic friction rub, synchronous with systole and diastole, was heard over the precordium. No definite murmur could be made out. The liver was four fingerbreadths below the right costal margin in the midclavicular line, and was smooth and tender. The spleen was two fingerbreadths below the left costal margin, and had a firm, round edge. There was moderate ankle and pretibial edema. The impression at this time was rheumatic heart disease, with mitral stenosis and congestive failure, and thrombophlebitis of the left internal jugular vein, with multiple infarcts in both lungs.

A roentgenogram of the chest showed that the cardiac shadow was enlarged in the transverse diameter and also toward the back, obliterating the retrocardiac space in the region of the left auricle and ventricle. The maximum heart measurements were 5.7 cm. to the right and 11.4 cm. to the left; the transverse diameter of the chest was 30.4 cm. The general appearance suggested mitral valvular disease. Multiple, dense shadows were scattered throughout both lungs, particularly the lower lobes; these were regarded as infarcts (Fig. 1).

The electrocardiogram showed a sinus tachycardia of 120 per minute. There were marked right axis deviation and inversion of the T wave in Lead IV. The P-R interval and QRS time were within normal limits.

The blood Wassermann and Kahn reactions were negative. Urine analysis showed nothing abnormal. The nonprotein nitrogen of the blood was 45 mg. per cent.

The icterus index was 25. On June 5, 1941, the erythrocyte count and hemoglobin were normal. There were 9,200 leucocytes, of which 83 per cent were neutrophils. On June 13, 1941, the leucocyte count was 25,500, with 84 per cent neutrophils. A blood culture was negative.

While in the hospital, the patient continued to have a low-grade fever, and showed little response to digitalization and mercurial diuretics. The swelling in the left supraclavicular and infraclavicular regions subsided to a large degree, and a firm, tender, cordlike structure was palpable beneath the left sternomastoid muscle. The cough became more frequent, and there were copious expectoration of bloody sputum and severe pain in the lower ribs. The patient became stuporous, lapsed into a muttering delirium, and died June 17, 1941.

The autopsy was performed by Dr. J. G. Pasternack, pathologist.

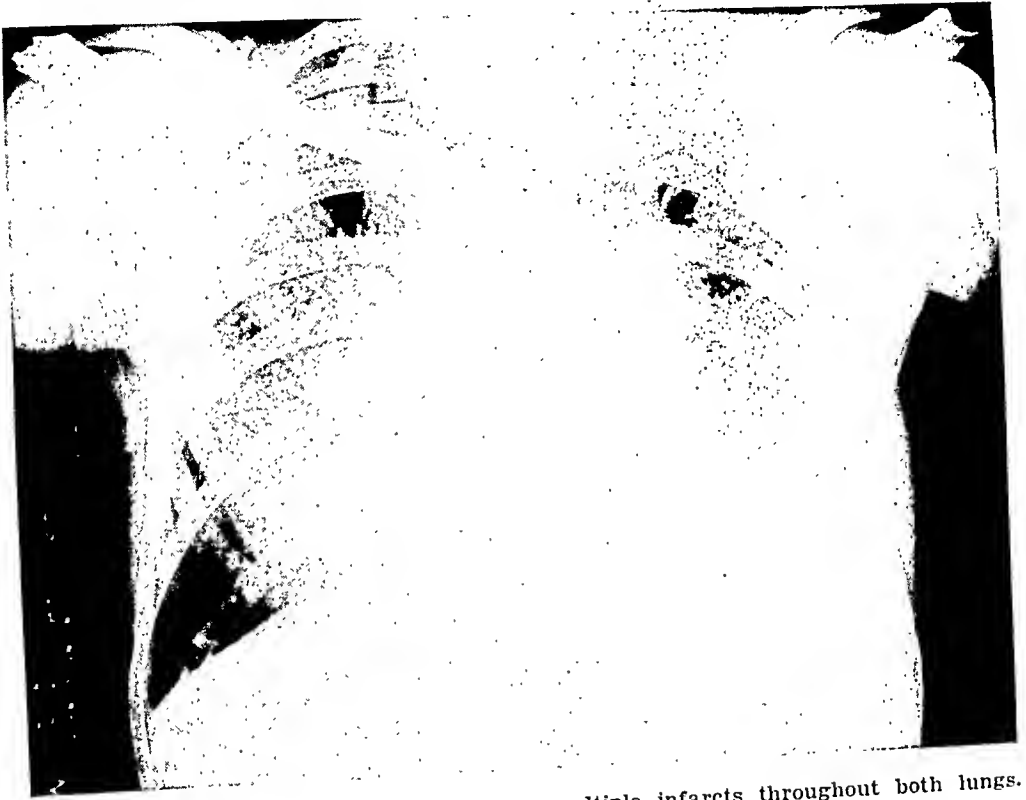


Fig. 1.—Roentgenogram of chest, showing multiple infarcts throughout both lungs.

The body was fairly well developed and nourished. There was a moderate degree of jaundice of the skin and sclerae. The left side of the neck showed fusiform bulging along the sternomastoid muscle. The peritoneal cavity was half filled with clear, straw-colored fluid. The liver was enlarged, firm, and smooth; the spleen was large and firmly adherent to the diaphragm. There were no adhesions to the sternal plate. The right lung was massively fixed in place by old adhesions which formed cystic spaces containing large quantities of hemorrhagic fluid. The left side of the chest was half filled with bloody fluid. The pericardial sac was greatly distended, and contained approximately 250 cc. of faintly turbid, straw-colored fluid.

The heart weighed 680 grams. The right atrium was approximately three times the normal in size, and the left atrium was probably ten times the normal in size and extremely thin. The pulmonary and tricuspid valves were normal. The musculature of the right ventricle averaged 8 mm. in thickness. The mitral orifice was markedly stenosed; it admitted an instrument $\frac{1}{2}$ cm. in diameter with difficulty. The mitral cusps were entirely replaced by old, deforming scar tissue and organized vegetations which were rough and hemorrhagic in appearance. At the

base of the valves there was marked calcification. The chordae tendineae were markedly sclerosed, as were the apices of the papillary muscle. The musculature of the left ventricle averaged 24 mm. in thickness. The aortic orifice was markedly stenosed; its circumference was slightly more than 3 cm. The cusps were adherent and greatly deformed by scar tissue. Their bases showed old sclerosis and calcification. The coronary ostia were deformed and stenosed as a result of advanced atheromatous changes in the aorta. The coronary arteries were patent.



Fig. 2.—Dissection showing massive thrombosis of left internal jugular vein.

There was massive thrombosis of the left internal jugular vein from the base of the skull to its junction with the left subclavian vein (Fig. 2). It was 5 cm. in diameter in its largest part. The thrombotic process extended for a short distance into the left innominate and subclavian veins, and also involved the thoracic duct. The thrombus in the internal jugular vein in its most distal portion was well organized, and inseparably fused with the wall of the vein for a distance of about 1 cm. upward. Beyond this point the organization was recent, and the thrombus could be separated from the vessel wall. The blood clot was apparently old.

The lungs together weighed 1,550 grams. The pleural surfaces showed old and recent fibrosis. Numerous firm infarcts were present in all the lobes of both lungs. On section, infarcts of various sizes, from less than 1 cm. to masses 6 cm. by 10 cm., were found throughout both lungs. Some were old and partly organized; others were red and hemorrhagic, and apparently of recent origin. The liver weighed 2,300 grams. On section the hepatic parenchyma showed an advanced nutmeg appearance.

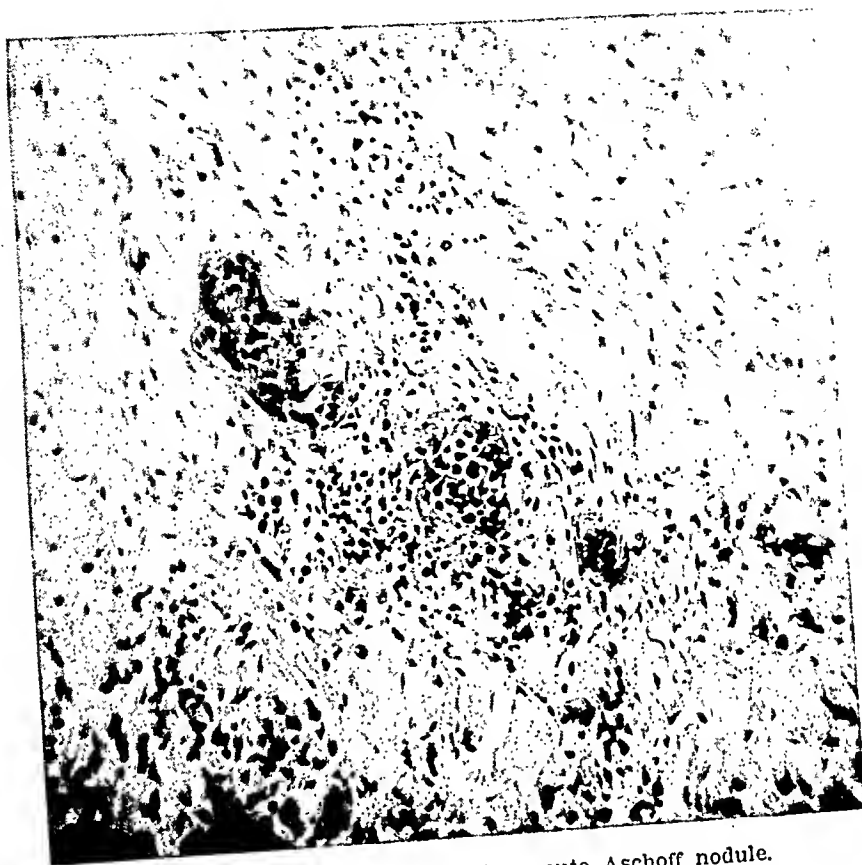


Fig. 3.—Wall of vein, showing acute Aschoff nodule.

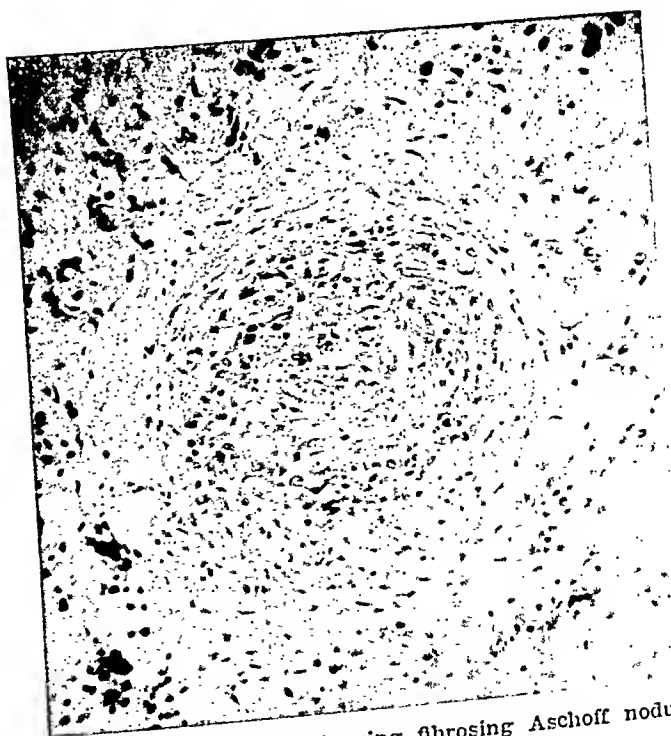


Fig. 4.—Wall of vein, showing fibrosing Aschoff nodule.

The anatomic diagnosis was chronic rheumatic valvulitis, mitral and aortic, massive thrombosis of the left internal jugular vein, multiple infarcts of both lungs, old and recent, bilateral fibrosanguinous pleuritis, chronic pleuritis on the right, hydropericardium, and hydroperitoneum.

MICROSCOPIC EXAMINATION

There were extensive areas of old and recent infarction in the lungs, and, in some sections, necrotic parenchyma in the process of suppuration could be seen. The heart showed old endocardial and pericardial fibrosis. No fresh vegetations were found on the heart valves. There were extensive, irregular, interstitial fibrosis and foci of old scarring in the myocardium.

The internal jugular vein showed massive thrombosis and thrombophlebitis. The normal architecture of the wall was entirely destroyed. The inflammatory reaction varied in different areas. Stretches of the intima showed thrombonecrosis and merged inseparably with the thrombus. In certain areas there was a granulating endophlebitic reaction, with more or less marginal organization of the thrombus. The media and adventitia showed extensive, active fibroplasia, fibrosis, and capillary vascularization. Here and there the vasa vasorum and capillaries showed fibrinous and fibrinopurulent thrombosis, massive thrombonecrosis, and granulating and fibrosing thromboangiitis, with recanalization or complete occlusion of the lumen. In some areas small blood vessels showed fibrinoid degeneration of their wall and perivascular fibroplasia, with dense infiltrations of plasma cells, monocytes, and eosinophiles. There were occasional, small, pseudogranulomatous foci formed of hypertrophied fibroblastic cells, plasma cells, and lymphocytes. A small central blood vessel, showing fibrinoid degeneration or fibrosis of its wall, was usually present. In other similar lesions the associated blood vessel showed fibrosing pseudogranulomatous panangiitis, with perivascular fibroblastic mantling and infiltration of plasma cells, monocytes, and eosinophiles. These lesions were regarded as fibrosing Aschoff nodules. Some of the nodules were more typical than others (Figs. 3 and 4).

COMMENT

Most authors have hesitated to accept the occurrence of venous thrombosis in rheumatism as secondary to definite phlebitis of rheumatic nature. This has been particularly the case when the thrombosis was observed as an incident to an apparently quiescent stage of the disease. Welch, among others, considered recent joint symptoms or active endocarditis essential to the diagnosis of rheumatic phlebitis, and, since he found a low incidence of both in his series, minimized the role of rheumatic infection. Sladen and Winternitz, likewise, believed that rheumatic phlebitis should be closely related to the active rheumatic state. Nevertheless, the chronicity and recurrent nature of rheumatism led them to acknowledge the possibility of a persistent focus within the vein which might ultimately lead to thrombosis. This concept is strengthened by the observations in our case, in which active carditis was absent at autopsy and joint symptoms had preceded venous thrombosis by many years.

Although it is true that venous thrombosis is a not infrequent complication of congestive heart failure, the latter is not a primary factor in all rheumatic cases. Remlinger¹⁹ has described a case of extensive venous thrombosis associated with acute articular rheumatism, without carditis.

Voelcker¹¹ likewise observed involvement of the femoral and saphenous veins in a case of chorea without apparent heart disease. These observations, together with the histologic changes described herein and previously recorded by Perry, indicate that rheumatic infection, per se, may be responsible for venous thrombosis.

It has been shown that the entire arterial system, from the aorta to the smallest of its ultimate divisions, may be involved by the virus of acute rheumatic fever.^{12, 13} The recognition of specific rheumatic lesions in the venous system tends further to emphasize the fact that widespread vascular damage may occur in this disease.

SUMMARY

1. A case of massive thrombosis of the left internal jugular vein complicating rheumatic heart disease is presented.
2. The histologic changes indicate that thrombosis was secondary to a definite phlebitis of rheumatic nature.
3. The absence of other clinical and pathologic signs of acute rheumatism strongly suggests that active infection persisted within the vein wall long after the acute phase of the disease had passed. The occurrence of venous thrombosis months or years after acute rheumatism, therefore, does not necessarily exclude the possibility of an underlying rheumatic phlebitis.

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POLYPOID THROMBUS OF THE LEFT AURICLE, WITH REPORT OF A CASE

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THE recent literature^{1, 2, 3} furnishes a few case reports of tumor masses of the auricles, most of which have been accepted as myxomas arising from the auricular septum. In the following case report the history is similar to that of previously reported myxomas, but the anatomic interpretation differs from that of other reported cases.

CASE REPORT

The patient entered the University Hospital* April 16, 1941, complaining of weakness, difficulty in walking, and speech defects. Since the patient was unable to speak distinctly and, in addition, understood and spoke English poorly, the history was not complete. The symptoms apparently began four months before the patient's admission to the hospital; first there were stiffness of the left hand and pain in the left shoulder. Then a speech defect developed; it was noted that the patient seemed to drag his words. During the second month of his illness the patient had two periods of unconsciousness; the nature of the attacks was not known. In the following months some disability of his upper extremities developed. No further history was obtained.

Physical examination revealed that the patient was not acutely ill. The temperature was 98° F., the pulse rate, 80, the respiratory rate, 20, and the blood pressure, 104/78. A marked arcus senilis was present. The pupils were slightly irregular, reacted slowly to light, and were constricted. The fundi were normal. A loud presystolic murmur was heard over the precordium; it was loudest at the apex and along the left sternal border. A thrill could be palpated at the apex of the heart. Moist inspiratory râles were noted at the bases of the lungs. Abdominal and rectal examination was negative. A hydrocele was present on the right.

Neurologic examination revealed that the patient responded slowly and poorly. He walked slowly, with a broad base, but there was no evidence of hemiparesis. The extraocular movements were normal save for a slight nystagmus on looking to the right. The right angle of the mouth was pulled back less than the left, and there was some smoothing of the face. The tongue protruded in the midline and was not atrophied. The reflexes of the biceps and triceps were exaggerated bilaterally, but more on the left. Hoffman's sign was positive on the left. There was some clubbing of the fingers, and there was marked spasticity of both upper extremities. The knee jerks were hyperactive, particularly on the left. The Babinski sign was negative.

Routine laboratory examinations showed that the blood, the urine, and the stool were normal. The sedimentation index was 1.63 mm./minute, with a hematocrit reading of 34 per cent. The electrocardiogram showed a small, notched QRS complex in all leads. Roentgenologic examination revealed that the skull was negative. Cardiac enlargement was present, and a minimal degree of infiltration was noted in each apex.

No diagnosis was made of the neurologic condition, and the patient was trans-

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ferred to the medical service for treatment of his suspected mitral rheumatic heart disease. The patient was digitalized and maintained on a dose of 0.1 Gm. of digitalis daily. On this medication the moist râles in the lungs cleared up. The final diagnosis was cardiac enlargement caused by mitral stenosis. Rheumatic fever was the suspected cause of the valve defect. Function was judged to be grade I. The patient was discharged from the University Hospital April 27, 1941, and advised to continue taking digitalis.

The patient was admitted to St. Mary's Hospital, Detroit, Aug. 27, 1941. It was learned from informants that the symptoms had become aggravated in the preceding four days. Information concerning the patient's course during the interval could not be obtained, and the patient was too ill to question.

Examination on admission to the hospital revealed a poorly nourished, extremely ill person. The temperature was 99° F., the pulse rate, 96, and the respiratory rate, 20. The blood pressure was not recorded. The patient was dyspneic and cyanotic. The pupils reacted poorly to light. Numerous coarse râles were heard over both lungs. The heart was enlarged to percussion, but no murmurs were heard. The patient had pronounced dependent edema and some ascites. The reflexes were hypoaactive. The patient failed rapidly, and died several hours after his admission to the hospital.

NECROPSY EXAMINATION

The autopsy was performed ten hours after death. The body was that of a well-developed, rather poorly nourished, white man. Mild pitting edema of the lower extremities was present. Approximately 2,000 c.c. of clear serous fluid were found in the peritoneal cavity. There were 1,500 c.c. of serous fluid in the left pleural cavity and approximately 500 c.c. in the right. The pericardial sac showed no abnormalities.

The heart measured 16 cm. in its greatest width. The weight of the unopened heart, containing the tumor and a few blood clots, was 560 grams. Examination of the descending branch of the left coronary artery revealed a moderate degree of sclerosis, but no points of occlusion could be detected. The recurrent branch and the right coronary arteries were normal in appearance. The ventricular muscle was flabby, and examination of the surface made by cutting revealed in the inferior half of the left ventricle numerous fibrotic patches measuring from 2 mm. to 5 mm. in diameter. No recent infarcts were seen. The root of the aorta was smooth; the right auricle and the right auricular appendage were normal.

Examination of the left auricle showed that it was bulbous in character, and portions of a tumor mass protruded from the cut ends of the pulmonary veins. The auricle was markedly dilated. Since the nature of the tumor was obvious, the left ventricle was opened and the tumor inspected through the mitral valve. It was seen to hang into the valve when the heart was suspended, and to slide to and fro in the auricle when the heart was manipulated; this movement might have occurred during the life of the patient. The left auricle was carefully opened along its lateral surface, and a soft, pale yellow, gelatinous tumor was seen almost filling the chamber. From the more firm central portions of the tumor, soft, friable, papillary processes protruded; many of these were easily broken from the tumor, even though it was handled gently. The entire mass was adherent by a narrow pedicle to the auricular wall approximately 3 cm. superior to the mitral valve. The tumor mass measured approximately 10 cm. in its widest diameter and about 4 cm. in thickness. Further examination of the heart revealed that all chambers were dilated. The valves were normal in appearance, and the vena cava, which was opened in its entirety, was also normal.

The right lung weighed 790 grams, and the left, 619 grams; their pleural surfaces were smooth, and both organs were brownish in color. A large amount of fluid exuded from their cut surfaces, and several infarcts were seen in the lower lobes. The liver weighed 1,824 grams, and examination of its cut surface revealed

a marked degree of chronic passive congestion. The total weight of the kidneys was 303 grams. Their cut surfaces appeared congested, and a well-defined infarct was seen in the superior pole of the right kidney. The remainder of the organs were normal. Unfortunately, permission to examine the brain could not be obtained.

The tissues were fixed in a 10 per cent solution of formalin and were stained with hematoxylin and eosin, Weigert's elastic tissue stain, van Gieson's stain, and Wilder's silver stain. In addition, several stains were used for mucin, including thionin, mucihematin, and Lillie's toluidine methylene blue.⁴

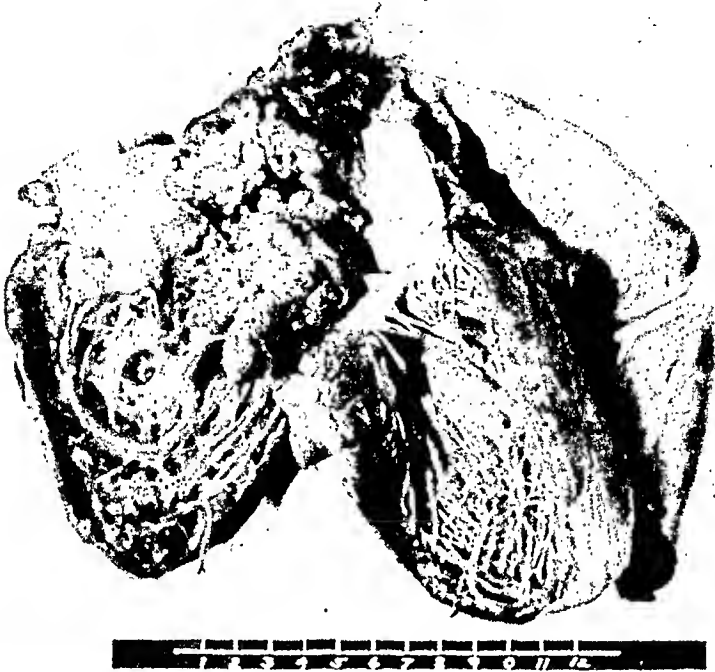


Fig. 1.—Polypoid tumor of opened auricle.



Fig. 2.—Section through septum. Note connective tissue bands extending from rounded auricular wall.

Examination of paraffin sections of the tumor showed that its papillary processes were covered by endothelium. In the hematoxylin and eosin stains the bulk of the tumor stained lightly with eosin and was relatively acellular. The stroma was interrupted by many irregular vascular channels, and many vacuoles were seen at

various points. Closer examination showed that the stroma was formed by delicate eosin-staining fibers embedded in a grayish ground substance. A few giant cells of the foreign body type hugged the vascular channels, and many erythrocytes and a few lymphocytes were noted here and there in the stroma. In the matrix there were a few large cells which were spindle-shaped and had large elliptical nuclei, with a moderate amount of chromatin. The cytoplasm of these cells was difficult to distinguish in most instances. Numerous macrophages filled with an iron-containing pigment were present throughout the entire tumor, but more were seen near and about the pedicle.

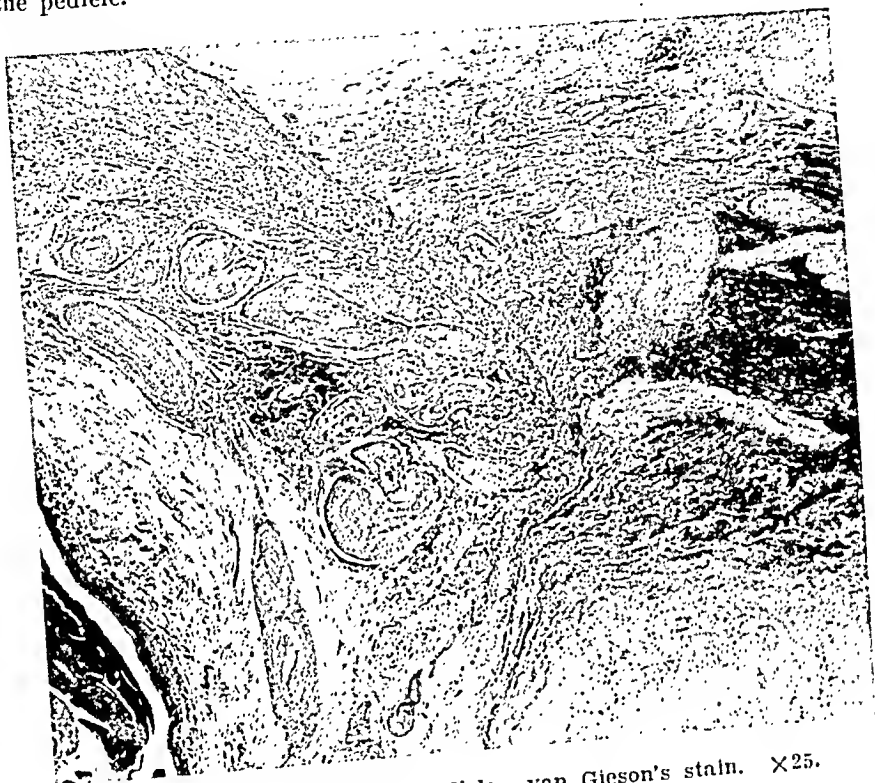


Fig. 3.—Section through pedicle. van Gieson's stain. $\times 25$.

Several sections taken directly through the pedicle revealed a marked increase in collagenous tissue immediately beneath the endocardium. Here there was a surprisingly large number of arterioles of various sizes, the smallest of which showed marked subintimal hyaline deposits, and the larger of which showed extensive intimal thickening, with almost complete closure of their lumens. In the latter vessels the picture was that of disuse atrophy. Numerous collagenous fibers were seen in the pedicle, and were found to be continuous with those of the auricular wall and to extend as armlike processes into the tumor. Many of the dense areas of collagenous fibers were separated by looser, somewhat myxomatous, tissue. Small arterioles in the proximal portions of the pedicle were also present. In the deeper portions of the pedicle, approximately 1 cm. from the auricle wall, the tumor was made up of looser connective tissue separated by myxomatous portions of the stroma. Reticular fibers were abundant throughout the tumor, but only a few, fine, elastic fibers were seen in sections stained by Weigert's method. The specific stains failed to give a positive reaction for mucin.

Examination of sections taken from the left ventricle revealed an increase in connective tissue beneath the endocardium. In many areas the myocardial fibers were replaced by collagen, and several recently healed infarcts were noted. The myocardial fibers appeared to be increased in diameter. The smaller branches of the coronary artery showed irregular intimal thickening. No evidence of rheumatic heart disease was apparent.

Sections of the lungs and liver showed advanced chronic passive congestion, and there were large areas of necrosis about the central veins of the liver. Sections of the spleen and kidneys revealed a moderate degree of passive congestion. No changes were noted in the small arterioles of the kidneys.

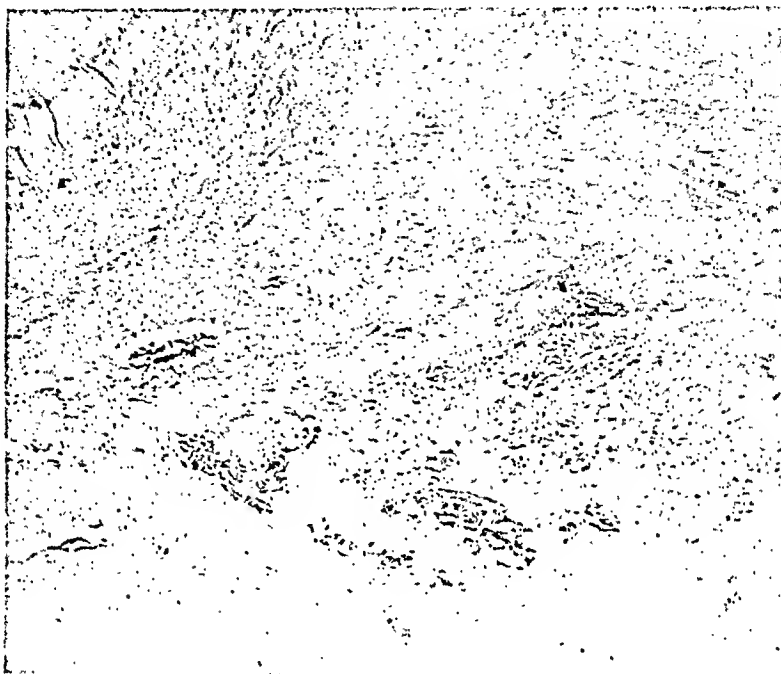


Fig. 4.—Section taken from periphery of tumor. Hematoxylin and eosin stain. $\times 25$.

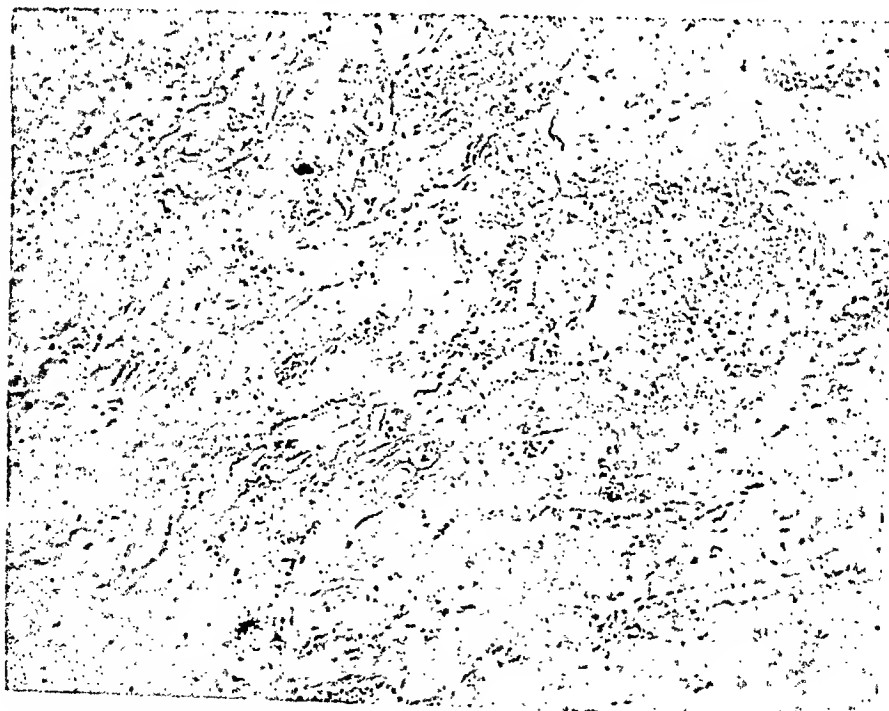


Fig. 5.—Section taken from periphery of tumor. Hematoxylin and eosin stain. $\times 100$.

DISCUSSION

Examination of this tumor indicated that the mass was not a myxoma, but was a pedunculated mural thrombus undergoing organization and retrogressive changes. The following is the evidence in favor of this thesis.

1. The observed coronary sclerosis, myocardial fibrosis, and cardiac hypertrophy, accompanied by congestive heart failure, may explain the formation of a thrombus.

2. The presence of injury to the auricular wall at the site of attachment of the pedicle is suggestive of a pedunculated mural thrombus.

3. The arteries of the auricular wall showed disuse atrophy, which would not be expected if a myxoma were growing from this site.

4. The structure of the pedicle and the central portion of the mass was that of an organizing thrombus, whereas the bulk of the tumor showed retrogressive changes.

5. The tumor failed to show the histologic features of a myxoma, nor did it give the characteristic stains for mucin.

The differences between organized thrombi and true myxomas have been discussed in several publications.¹ In the majority of the previous case reports, detailed studies of the pedicles of the tumors have not been recorded, but coronary sclerosis, with areas of myocardial fibrosis, has been seen.² Since the history and the gross appearance of the tumor were similar to the history and gross appearance in many previously described cases, it is possible that some of the auricular masses may not be true myxomas. Careful study will probably show that many pedunculated tumors of the auricles are, as Warthin has shown,⁵ organizing thrombi.

SUMMARY

1. A primary tumor of the left auricle is reported.
2. Anatomic studies of the tumor would indicate that the mass was an organizing thrombus originating from the interauricular septum.

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ELECTROCARDIOGRAMS SIMULATING THOSE OF CORONARY THROMBOSIS AFTER CESSATION OF PAROXYSMAL TACHYCARDIA

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THE occurrence of transient abnormalities of the T wave of the electrocardiogram after the cessation of paroxysmal tachycardia has recently been emphasized by Campbell¹ in a report of several instances in which some flattening, and even inversion of this deflection was noted for days after paroxysms, in subjects who gave no other evidence of cardiovascular disease. The earliest allusion to such phenomena appears to be that of Graybiel and White,² who briefly mentioned two instances in a report dealing with inversion of the T waves associated with a variety of essentially noncardiac disorders.

We have encountered such abnormalities on two occasions in a subject whose several electrocardiographic abnormalities were so extreme in degree and prolonged in duration that the case was considered sufficiently remarkable to be placed on record.

CASE REPORT

M. T. (Unit No. 18626), a 38-year-old policeman, ate a large dinner of corned beef, cabbage, and turnips, and immediately afterward developed epigastric distress, together with rapid beating of the heart and a mild smothering sensation. His symptoms, which persisted throughout the night, were not sufficiently disturbing to prevent his spending the evening out with friends and indulging in several highballs and a midnight luncheon, but he slept poorly after retiring. The next morning he visited his doctor, who administered a white pill every three hours, but the tachycardia persisted all day, and the patient grew sufficiently uncomfortable to apply for admission to the New Haven Hospital, on Jan. 25, 1932.

The patient had not had similar symptoms before, and he had always considered himself in vigorous health. He smoked in excess of a package of cigarettes daily.

Examination in the hospital revealed a youthful-appearing man with slight cyanosis of the lips, hands, and feet. The neck veins were slightly distended in the sitting position. The heart sounds were of good quality, but the rate was extremely rapid, and a pulsation synchronous with the heart beat was visible in the epigastrium. The blood pressure was 95/80. The edge of the liver reached about 3 cm. below the costal margin. A few rales were heard in the base of the right lung. The electrocardiogram confirmed the clinical impression of paroxysmal tachycardia; the ventricular rate was 230 (Fig. 1, A). The leucocyte count was 13,800, with 80 per cent polymorphonuclear cells. The temperature was 101° F. by rectum.

Pressure upon the carotid sinus region, eye balls, and epigastrium did not influence the heart rate, and vomiting induced by ipecac was also ineffectual. Quinidine sulfate was administered orally, therefore, in a test dose of 0.2 Gm., followed by another dose of 0.2 Gm. in ninety minutes. A third dose of 0.4 Gm., given three

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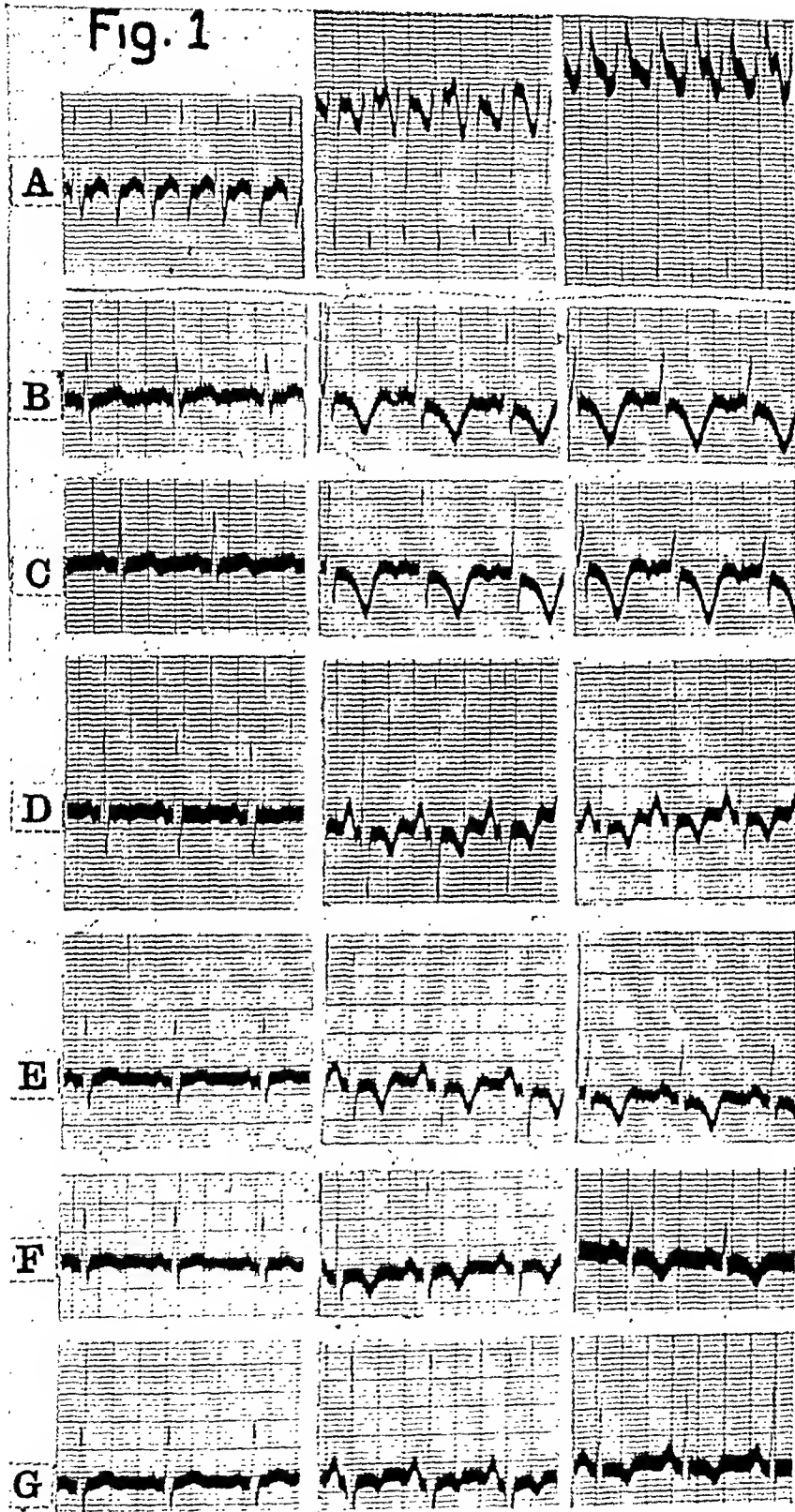


Fig. 1.—Leads I, II, and III from left to right. *A* shows paroxysmal tachycardia with a rate of 230; the paroxysm lasted about forty-four hours. *B* and *C* were obtained on the first and second days, respectively, after termination of the paroxysm, and *D*, *E*, *F*, and *G* were obtained on the ninth, sixteenth, twenty-third, and thirty-seventh days, respectively, after termination of the attack.

hours later, was followed in about an hour by sinus rhythm with a rate of 100. This terminated a paroxysm that had lasted about forty-four hours. Within a few hours all the symptoms and the physical abnormalities had disappeared, the blood pressure was 125/85, the leucocyte count had fallen to 8,750, with 50 per cent polymorphonuclear cells, and the temperature had become normal.

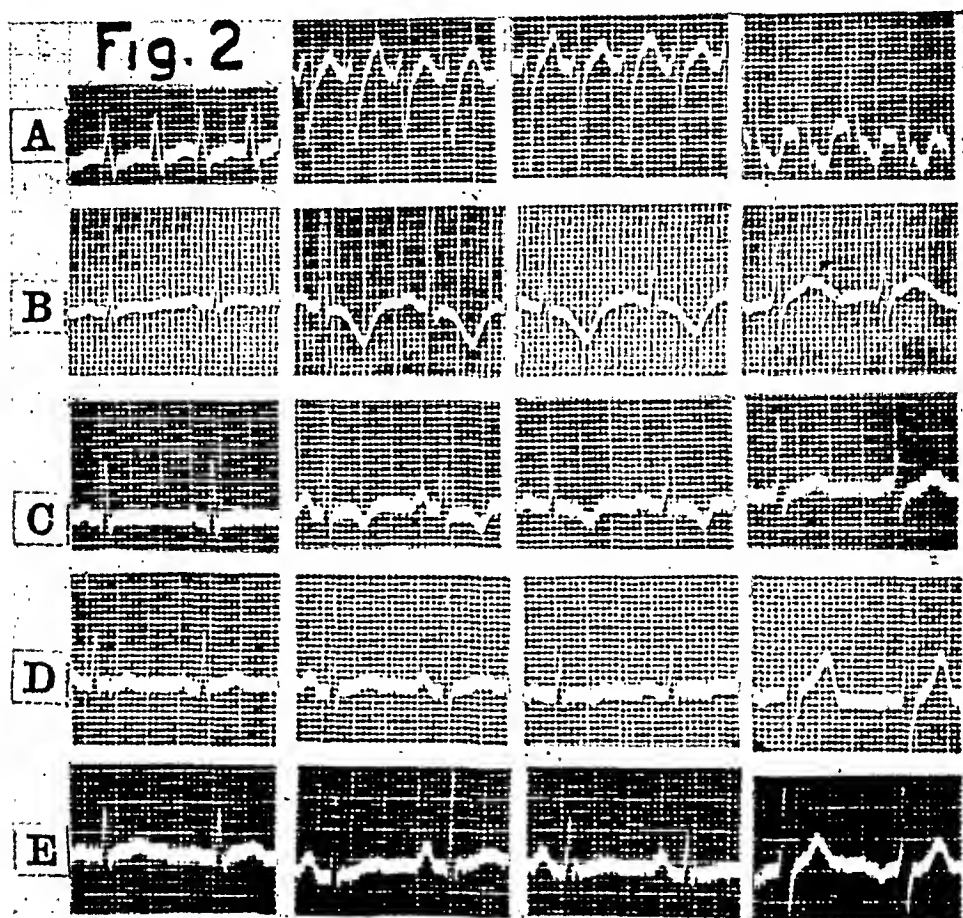


Fig. 2.—Leads I, II, III and IV F from left to right. A shows paroxysmal tachycardia with a rate of 200; the paroxysm lasted at least nine hours (not longer than nineteen). B was obtained within an hour of termination of the paroxysm, and C, D, and E were obtained twelve, twenty-six, and forty days later.

Just prior to the patient's discharge, on the following day, a routine electrocardiogram was obtained (Fig. 1, B), and this unexpectedly revealed T waves of an unusually wide and deeply inverted contour in Leads II and III, with slight depression of the associated RS-T segments; additional features of interest were low amplitude and deformity of the P waves, and abnormally long Q-T duration: the value for "K" was 0.509, as against the normal maximum value of 0.392.³ Although the electrocardiographer raised the question of coronary thrombosis, the patient had already left the hospital, and insisted on continuing his normal activity, for he felt entirely well. He agreed, however, to present himself for follow-up examinations, and during the ensuing thirty-five days the five additional electrocardiograms shown in Fig. 1 were obtained. It is noteworthy that abnormalities of the T waves persisted throughout this period, but the depth of the inversion diminished gradually, the P waves became prominent upright deflections, and the Q-T duration regressed to the low normal value of 0.34 for "K."

Ten years later, on the morning of Sept. 25, 1942, the patient walked into the emergency room with another paroxysm of tachycardia which had been present on arising that morning. He complained only of palpitation and faintness. Except for two brief attacks of palpitation several years before, he had been in seemingly excellent health during the decade between visits. The blood pressure was 95/60, the edge of the liver was several centimeters below the costal margin, and a few râles were heard in the base of the right lung. The electrocardiogram (Fig. 2, A) confirmed the diagnosis of paroxysmal tachycardia of supraventricular origin. Again, after several hours of rest, during which repeated trials of the usual pressure maneuvers failed to terminate the paroxysm, 1 Gm. of quinidine sulfate was given in divided doses over a period of about three hours. Within half an hour after the last dose, and not less than nine hours after the onset of the paroxysm, normal sinus mechanism suddenly returned, and the patient was quickly relieved of his symptoms and signs. Again, the posttachycardia electrocardiogram (Fig. 2, B) showed pronounced inversion of the T waves in Leads II and III, with flattening in Lead I; and again the P waves were deformed and the Q-T duration abnormally long, with "K" equal to 0.535.

The patient was discharged the same day, and advised to take 0.2 Gm. of quinidine three times daily for two days. He returned to work immediately, but again cooperated in a protracted electrocardiographic follow-up study of his case. The three records subsequently obtained at fortnightly re-examinations over a forty-day period again showed persistence of the abnormalities for at least twelve days, with ultimate restoration of normal P and T waves and Q-T segments in the tracing taken on the twenty-sixth day after the paroxysm (Fig. 2). The patient continued asymptomatic and actively at work. The blood pressure was consistently about 115/75, the heart remained normal to auscultation, and the cardiac configuration and size were still normal on fluoroscopic examination at the time of the last electrocardiogram.

COMMENT

Because auricular paroxysmal tachycardia is encountered commonly in young adults, often under conditions of stress, but usually in the absence of demonstrable heart disease, its relatively frequent occurrence in military and wartime industrial life is to be anticipated. Since the more severe attacks draw attention to the heart, and may sometimes simulate coronary thrombosis clinically, the fact that the electrocardiogram may be grossly abnormal for days and weeks after the attack may mislead the physician into a diagnosis of a grave myocardial lesion; in fact, one of Campbell's cases was that of a member of the Royal Air Force who had been hospitalized for six weeks under the suspicion of "myocarditis."

The striking prominence and depth of the T-wave abnormalities and their long persistence after acute cardiac attacks might readily lead to an erroneous diagnosis of myocardial infarction, with the imposition of an unnecessarily long convalescence, the pronouncement of a needlessly bad prognosis, and perhaps ill-advised retirement from active service. That such a diagnosis is untenable in the case described would appear certain from the fact that the patient had no cardiovascular symptoms whatever in the ten years between the two recorded attacks,

that the clinical course after each attack was not that of acute coronary thrombosis, and that the normal electrocardiographic pattern was not only entirely restored, but was regained in too short a time for myocardial infarction to have occurred; moreover, detailed study of the abnormal records reveals certain differences between them and the classical picture of acute myocardial infarction, such as *depression* of the RS-T segments in the leads with inverted T waves, and failure of abnormal Q waves to develop.

How may these extraordinary abnormalities be explained? Although quinidine is known to produce changes in the final deflection of the ventricular complex, the brief exhibition of the drug and the small doses given this patient cannot account for the persistence of the abnormalities over a period of weeks. One may offer the hypothesis that the changes resulted from myocardial ischemia associated with a sharply diminished cardiac output during the many hours of the unusually high ventricular rate of the paroxysms. A common antecedent factor in the few reported instances of these strange effects has been the relatively long duration of the paroxysm that preceded them. A causal relationship to time is suggested by the observation in our case that the abnormalities regressed about twice as rapidly after the second paroxysm, which was less than half as long as the first. The persistence of the abnormalities for several weeks would seem to imply that some injury to the heart muscle had occurred, but the ultimately complete electrocardiographic and clinical recovery suggests that the injury was of a reversible nature, and did not lead to death of tissue. Whatever the true explanation, the evidence at hand would indicate that the electrocardiographic developments represent a transient and probably benign incident associated with paroxysmal tachycardia, and their recognition should prevent a too ready and dogmatic diagnosis of coronary thrombosis.

Last, but not least, another cause for inversion of T waves must be added to the already long but still growing list.

SUMMARY AND CONCLUSIONS

Pronounced electrocardiographic abnormalities simulating myocardial infarction, and lasting for several weeks, were encountered in two series of electrocardiograms taken after attacks of paroxysmal tachycardia in a man who appears to have no structural disease of the heart. The abnormalities probably represent benign, functional changes, and they should not be mistaken for evidence of coronary thrombosis. The observations add another item to the list of causes for abnormal T waves.

ADDENDUM

Since the acceptance of this paper for publication, two other relevant reports have come to the author's attention. The first was that of P. Cossio and his associates (Rev. argent. de cardiol. 8: 168, 1941), and

the other was a case report by G. M. Currie (Brit. Heart J. 4: 149, 1942). Of the five patients described, one died, and necropsy revealed some cardiac dilatation but no abnormality of the coronary vascular system and no focal myocardial lesions.

REFERENCES

1. Campbell, M.: Inversion of T Waves After Long Paroxysms of Tachycardia, Brit. Heart J. 4: 49, 1942.
2. Graybiel, A., and White, P. D.: Inversion of the T-wave in Lead I or II of the Electrocardiogram in Young Individuals With Neurocirculatory Asthenia, With Thyrotoxicosis, in Relation to Certain Infections, and Following Paroxysmal Ventricular Tachycardia, AM. HEART J. 10: 345, 1934.
3. New York Heart Association Criteria Committee: Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, 1939, N. Y. Tuberc. & Health Assoc.

Abstracts and Reviews

Selected Abstracts

Essex, H. E., Herriek, J. F., Mann, F. C., and Baldes, E. J.: The Effect of Atropine on the Coronary Blood Flow of Trained Dogs With Denervated and Partially Denervated Hearts. *Am. J. Physiol.* 138: 683, 1943.

In the present study, the response of the coronary blood flow and heart rate to atropine sulfate has been observed after the following operative procedures: (1) right and left sympathetic ganglionectomy from the eighth or ninth intercostal space anteriorly, including the stellate ganglion; (2) double vagotomy in the neck; (3) a combination of procedures 1 and 2. In the absence of the sympathetic nerves, as in procedure 1, atropine caused increases of 25 to 85 per cent in coronary flow, and an increase in pulse rate of a similar magnitude. Atropine was without effect on the coronary blood flow, heart rate, or blood pressure of vagotomized animals, or animals with denervated hearts. It may be concluded that the increased coronary blood flow following injections of atropine is not owing to a direct effect of the drug on the wall of the blood vessel, nor is it due to changes of blood pressure. The augmented coronary flow follows the inhibition of vagal tone, and is associated with the resulting increased cardiac rate. When all of the evidence is considered, it is difficult to escape the conclusion that the increased heart rate itself is responsible for the increased coronary blood flow following administration of atropine, but the mechanism by which it is accomplished is not apparent.

AUTHORS.

Pochin, E. E.: Edema Following Ischemia in the Rabbit's Ear. *Clin. Sc.* 4: 341, 1942.

If the circulation to the rabbit's ear is arrested for eighteen hours and then released, massive edema develops within two hours.

The edema may subside in a few weeks, or, when ischemia has been at a higher temperature or has been of longer duration, it may terminate in dry gangrene.

The protein concentration in the edema fluid is initially about 5 per cent, but falls progressively.

AUTHOR.

Levy, H., and Boas, E. P.: Angina Pectoris and the Syndrome of Peptic Ulcer. *Arch. Int. Med.* 71: 301, 1943.

Certain relations between the syndromes of angina pectoris and peptic ulcer are described. It is suggested that neurogenic mechanisms mediated by the vagus nerve are concerned in this association.

AUTHORS.

Garvin, C. F.: Cardiac Cirrhosis. *Am. J. M. Sc.* 205: 515, 1943.

Of 790 consecutive, adult, autopsied patients who died of heart disease, thirty-five (4.4 per cent) had cardiac cirrhosis. Only those cases were included in which there was actual architectural distortion of the liver.

Cardiac cirrhosis occurred essentially in two types of heart disease, viz., rheumatic heart disease (fourteen of 119 cases), and hypertensive heart disease (fourteen of 264 cases).

From a clinical standpoint, there was a tendency for the cases of cardiac cirrhosis to be associated with multiple episodes of failure, ascites, splenomegaly and, in the rheumatic group, with tricuspid stenosis. In five of the thirty-five cases studied, the diagnosis was suspected clinically. It appears that there are no definite criteria, however, which permit the consistent clinical diagnosis of cardiac cirrhosis.

AUTHOR.

Cooke, W. T., and White, P. D.: Paroxysmal Ventricular Tachycardia. *Brit. Heart J.* 5: 33, 1943.

The authors have reported twenty-seven cases of ventricular paroxysmal tachycardia. Twenty-four of these were found in a review of 51,000 plates and films taken on about 25,000 patients in the Cardiographic Laboratory of the Massachusetts General Hospital, over a period of twenty-five years, from 1914 to 1939.

The criteria for diagnosis were the electrocardiographic findings. Fulfillment of any one of the following four points justifies the diagnosis.

1. The presence of P waves at a slower rate than that of abnormal QRS waves during the paroxysm of tachycardia.
2. A paroxysm of abnormal ventricular complexes, that is, three or more, occurring during auricular fibrillation.
3. The onset of tachycardia with an abnormal ventricular complex.
4. Close resemblance of the complexes of ventricular premature beats to the complexes occurring during paroxysmal tachycardia.

Coronary heart disease was present in twenty-two of our twenty-seven cases; four had apparently normal hearts; and one was thought to have a congenital ventricular septal defect. There were seventeen males and ten females, the youngest being aged 18 years and the oldest eighty-one years.

Digitalis had been administered to thirteen of the twenty-seven cases before the onset of tachycardia. It was probably the chief etiological factor in at least five of these cases.

It is suggested that abnormalities of the ventricular complexes of premature beats are responses to stimuli arising in the A-V node or bundle or main branches, at a point in the cardiac cycle when the conducting tissues are still partially refractory. The onset of ventricular tachycardia was generally in the part of the cycle that has been associated with the supernormal phase. The mechanism of ventricular tachycardia with alternating complexes may be due to abnormalities in conduction along the bundle branches in response to impulses arising in the A-V node.

The prognosis is generally, but not always, poor. Only two patients with coronary heart disease survived longer than two years from the first attack. Five patients with hearts otherwise normal have survived to date, periods varying from two to fifteen years.

Quinidine or quinine should be used in adequate dosage in the treatment of the attack, being given either by mouth, intramuscularly, or intravenously. Quinidine sulfate is most conveniently given by mouth in the dosage of 6 to 9 grains every two hours for five to six doses, under close observation and preferably with electrocardiographic control. If quinidine fails, quinine dihydrochloride, grains $7\frac{1}{2}$ subcutaneously, every two hours, is recommended to stop the paroxysm, and even to save life. A daily maintenance dose of quinidine by mouth (3 grains of the sulfate, four times a day) may be continued for prophylactic purposes for an indefinite time.

AUTHORS.

Ungerleider, H. E., and Gubner, R.: Extrasystoles and the Mechanism of Palpitation. *Tr. Am. Therap. Soc.* 41: 1, 1942.

An analysis was made of 1,142 cases with extrasystoles in order to determine their clinical significance. In 58 per cent, no objective evidence of heart disease was found.

Ventricular extrasystoles occur with considerably greater frequency than supraventricular premature contractions, and in the presence of heart disease there is a still greater preponderance of ventricular premature contractions.

Several factors, which are discussed, increase the significance of premature beats. Among these are the occurrence of premature beats of multifocal origin; frequent and persistent premature beats, particularly if they occur successively in short runs interrupting the regular rhythm; a definite increase in the number or shower of extrasystoles immediately following exercise; occurrence of premature contractions in the presence of a rapid heart rate; inversion of the T wave in the regular beat which follows the extrasystole; and postextrasystolic pulsus alternans.

Palpitation is a very common symptom often associated with extrasystoles. It has been generally attributed to an increased forcefulness of the regular beat following the premature systole, but several reasons are presented which indicate that this explanation is not tenable. It is suggested that palpitation occurring with premature contractions or tachycardia is due to, or associated with, an increased intensity of the first heart sound resulting from a more forcible closure of the arterio-ventricular valves. The symptom of palpitation is of no particular significance, and occurs in normal subjects as well as in those with heart disease.

AUTHORS.

Campbell, M.: Partial Heart Block With Dropped Beats. *Brit. Heart J.* 5: 55, 1943.

Partial heart block with dropped beats is nearly always transient, so that it is rare to find a patient in whom this rhythm can be expected as a usual or even a common finding.

At one time or another it was observed in nearly one-sixth of a series that included all types of heart block, but this gives an exaggerated idea of its frequency because it was generally transient and of short duration.

In two-thirds of the cases (twenty-five out of thirty-eight) there was a known cause, active infection or treatment with digitalis. In fourteen the cause was an acute infection, in five it was treatment with digitalis, and in six both causes combined. As would be expected, acute rheumatism was the most common infection (nine of twenty cases); but tonsillitis, without any suggestion that it was rheumatic, was often found.

The patients with dropped beats due to infections were mostly between 18 and 34 years of age. The outlook in this group was surprisingly good and the patient often recovered, even to the stage of a normal P-R interval. As an exception, the simultaneous association of tonsillitis and hyperthyroidism with dropped beats seemed of grave significance.

In the remaining third (thirteen cases) there was chronic heart disease and no very obvious reason why the dropped beats should have been found at the time they were, for here, too, they were generally transient. These were older patients, nearly all well over 60 years of age: all had chronic heart disease; high blood pressure and coronary atheroma were each the etiological factor in one-third, and in the remaining third there was myocardial disease without evidence of either of these factors.

In addition, some degree of heart block generally remained in the group of older patients, half of them having 2:1 heart block as a common or as their most usual rhythm. This was not so with the younger patients. Complete heart block also was uncommon in the group of younger patients with infections, but was present at some time in about one-fourth of the older group. The regular sequence of dropped beats, 2:1 heart block, and, finally, complete heart block were observed, but were rare.

The length of the P-R intervals was also studied. Progressive lengthening, but with a decreasing increment, was the rule, the increase of the second P-R interval over the first being much larger than the subsequent increases. There were, however, exceptions. In about one-eighth of the cases with dropped beats, these came without any gradual lengthening of the P-R interval (Hay's depression of excitability); these patients were mostly older ones with chronic heart disease.

For each grade of heart block up to a dropped beat after six responses, there were enough records to give some average figures, which are as follows:

- 3:2 heart block; 0.23, 0.35 second, dropped beat
- 4:3 heart block; 0.23, 0.30, 0.35 second, dropped beat
- 5:4 heart block; 0.23, 0.285, 0.32, 0.35 second, dropped beat

It must, however, be repeated that these are only the average of figures that varied widely in the different cases. It is strange that the average and the range of the P-R intervals between the first response after and the last response before the dropped beat should be so constant, whether there is one dropped beat to three, four, five, or six responses. This finding and some of the other points that have been discussed suggest that the defect of conductivity is generally the condition which makes heart block likely, but that something else, probably excitability, decides if there will be block, and, if so, of what grade it will be.

AUTHOR.

Carrillo, E. G.: A Fatal Case of Tachycardia and Paroxysmal Dyspnea in an Infant. *Rev. argent. de cardiología*. 9: 247, 1942.

The observation is recorded of an infant whose death, after a few hours of illness, seemed to be due to acute pulmonary edema. A great cardiac acceleration to 214 per minute was present clinically, and electrocardiographically resembled supra-ventricular paroxysmal tachycardia.

AUTHOR.

Walker, C. W.: Pregnancy and Labor in a Case of Congenital Coarctation of the Aorta. *Brit. M. J.* 1: 190, 1943.

The decision to allow labor to continue rather than have early recourse to cesarean section was prompted by the following considerations: The patient felt strong and well, was calm and confident, and was anxious to make the attempt; the infant was small and its presentation normal (L.O.A.), so that its passage might reasonably be expected to be an easy one; the early progress of cervical dilatation was free from fatigue and cardiac distress. In spite of these favorable circumstances the labor had to be stopped as soon as second-stage pains set in, as it was obvious that the tension in the upper circulation was being dangerously raised. With a full-term child, a less favorable presentation, a maternal heart having less reserve, or in the presence of more distressing first-stage pains, the danger point might well be reached before dilatation was complete and delivery possible. This being so, it would appear that in cases of coarctation of the aorta, however favorable, the obstetrical procedure of choice is cesarean section at the onset of labor.

AUTHOR.

Hansen, A. E., Platon, R. V., and Dwan, P. F.: Prolonged Use of a Sulfonamide Compound in Prevention of Rheumatic Recrudescences in Children: An Evaluation Based on a Four-Year Study on Sixty-Four Children. *Am. J. Dis. Child.* 64: 963, 1942.

A sulfonamide compound (sulfanilamide or, in a few instances, sulfathiazole or sulfadiazine) was administered to 53 different children for a total of 78 season cases to determine their value in preventing the occurrence of active rheumatic cycles, and the results were compared with those observed in 32 control children followed for a total of 46 season cases. All subjects studied were between 3 and 16 years of age, and had had essentially similar histories as regards previous rheumatic episodes, degree of cardiac involvement, and social status. These children were observed under conditions which closely approximate those encountered in the private practice of medicine. Only two of the 53 children in the group treated with a sulfonamide compound experienced a rheumatic flare-up, and in one this occurred within six days after the use of the drug was begun. On the other hand, 17 of the 32 children in the control group had a total of 21 rheumatic recrudescences. Eight of these recurrences were considered moderately severe; seven were mild, and in six of the subjects attacks of chorea were noted. In addition, the treated patients seemed favorably affected as regards the trend in degree of cardiac involvement, size of the heart, and functional classification. No difference was noted in the number of infections of the upper respiratory tract in the two groups, whereas the treated patients as well as the patients in the control group gained, and from a clinical viewpoint tended to be in better condition. Toxic manifestations due to the drug and disturbances in blood cells were seldom encountered, although during the fourth season the use of sulfathiazole was discontinued for one patient when the number of leucocytes dropped to 1,700. Improvement in the electrocardiographic tracings, though suggestive in several instances, could not be attributed to the effects of the drug alone. There was no evidence that the sulfonamide compounds produced changes in the electrocardiograms which may have been interpreted as being deleterious.

Although this series of cases is relatively small, the results are consistent, and, when interpreted in the light of observations of other investigators on this subject, appear to justify further study of the practical value of sulfonamide compounds in preventing rheumatic recrudescences. This appears to be especially true when we are aware that this disease is one of the major causes of disability and death in children of school age in the temperate zone. Caution should be the rule, and each child so treated should be under the care of a scrutinizing physician at all times.

AUTHORS.

Hansen, A. E.: Conditions Causing Confusion in the Diagnosis of Rheumatic Fever in Children: Analysis of Diagnoses Made by Practicing Physicians in 271 Rheumatic Subjects. *J. A. M. A.* 121: 987, 1943.

In the attempt to determine which disorders in children tend to be confused diagnostically with rheumatic fever, a study was made of the diagnoses given by practicing physicians and resident staff members with regard to 271 children with rheumatic fever who were admitted to the inpatient and outpatient cardiac disease clinic of the Department of Pediatrics of the University of Minnesota from 1928 to 1941. There was essential agreement in diagnosis in two-thirds of the cases. Review of the records of the remaining cases revealed that the conditions which caused most difficulty in the diagnosis of rheumatic fever under these conditions were: abdominal pain with possible appendicitis (about one-fourth of the cases studied); acute anterior poliomyelitis; acute osteomyelitis; erythematous or purpuric skin eruptions;

evidences of acute nephritis; acute fulminating illness (sepsis, pneumonia, subacute bacterial endocarditis); low-grade infections; and nervousness in mild chorea minor.

In order that the advantage gained by the early diagnosis and treatment may be realized to the fullest extent, the physician who is called on to care for children should be thoroughly familiar with the various and diverse manifestations of rheumatic fever.

AUTHOR.

Quinlan, J. T.: Sudden Death in Unsuspected Rheumatic Carditis. *Brit. M. J.* 2: 695, 1942.

A case of rheumatic carditis occurring in an apparently healthy infant, age 2 years, 8 months, is recorded. The post-mortem examination of the heart showed general enlargement as well as rheumatic mitral and tricuspid valvulitis. The finding of characteristic Aschoff bodies was accepted as proof of the rheumatic nature of the infection, and the other components of the microscopic picture provided additional evidence in support of this conclusion.

McCulloch.

Roberts, J. E., and Lisa, J. R.: The Heart in Pulmonary Tuberculosis: A Clinico-Pathological Study of 100 Autopsied Patients. *Am. Rev. Tuberc.* 47: 253, 1943.

The findings in a clinico-pathological study of the heart in 100 cases of active pulmonary tuberculosis are presented. Demonstrable myocardial lesions were present in sixty-nine. They consisted of tuberculous myocarditis in ten, acute rheumatic myocarditis in one, Aschoff body-like lesions in nine, acute interstitial myocarditis in fifty, and acute miliary infarctions in eleven. Combinations of the lesions were found in thirteen. Healed rheumatic valvulitis was found in five, sclerotic lesions of the mitral and aortic valves in twenty, acute valvular endocarditis in two, and syphilitic aortic valvulitis in two. There were three instances each of tuberculous, chronic adhesive, and acute nontuberculous pericarditis. Tuberculous myocarditis was more frequent in the adults than in the children. Nontuberculous pulmonary infections appeared to be a significant factor in the causation of the interstitial myocarditis. Miliary infarctions occurred predominantly in the hypertrophied hearts, in hearts with severe coronary arteriosclerosis, and in the later decades of life. The conception of a small heart in tuberculosis was not substantiated. Right ventricular hypertrophy was very uncommon. Mensuration of the ventricular wall appeared to be an unreliable criterion for hypertrophy; the microscopical appearance of the myocardial fibers appeared more accurate. A moderate or severe disproportion between pulse rate and height of temperature was suggestive of myocardial disease. Murmurs due to organic valvular lesions were fairly common. Functional murmurs were uncommon. The conception that hypertension and active tuberculosis are incompatible was not borne out. Electrocardiographic tracings frequently revealed significant observations. While the present series is too small to permit definite conclusions about many controversial points, it is the belief of the authors that more attention paid to the cardiovascular system in the tuberculous individual will result in a more accurate estimation of existing cardiac damage.

AUTHORS.

Suzman, S.: Tuberculous Pericardial Effusion. *Brit. Heart J.* 5: 19, 1943.

A case of tuberculous pericarditis is described. It is suggested that in any obscure case of pericardial effusion, especially where this is large, tuberculosis should be thought of as a possible diagnosis, and that this is still more likely if tapping has to be repeated.

Among 1,893 consecutive autopsies there were six cases of tuberculous pericarditis, but only one of these had been diagnosed clinically. Hemopericardium did not occur in any of these cases. Some excess of pericardial fluid was found in about one-fourth of all the tuberculous cases.

AUTHOR.

Goldblatt, H., Kahn, J. R., and Lewis, H. A.: Studies on Experimental Hypertension. XIX. The Production of Persistent Hypertension in Sheep and Goats. *J. Exper. Med.* 77: 297, 1943.

Persistent hypertension has been produced in the goat and sheep by constriction of the main renal arteries. The presence or absence of accompanying uremia depends upon the degree of constriction of the renal arteries.

In both sheep and goat, constriction of one main renal artery also caused elevation of the blood pressure, which tended to persist longer than in the dog. Excision of the one kidney with main renal artery constricted resulted in a prompt (twenty-four-hour) return of the blood pressure to normal.

In the animals with hypertension of long duration but without renal excretory insufficiency (the "benign" phase) no significant arterio- or arteriosclerosis developed as a result of the hypertension alone. In the animals that had both hypertension and renal excretory insufficiency (the "malignant" phase) the typical terminal arteriolar lesions developed in many organs. These lesions consisted of necrosis and fibrinoid degeneration of arterioles and necrotizing arteriolitis which should not be confused with arteriosclerosis.

The same humoral mechanism which is responsible for experimental renal hypertension in the dog and other animals also obtains in the pathogenesis of experimental renal hypertension in the sheep and goat.

AUTHORS.

Goldblatt, H., Katz, Y. J., Lewis, H. A., and Richardson, E.: Studies on Experimental Hypertension. XX. The Bioassay of Renin. *J. Exper. Med.* 77: 309, 1943.

A simple, rapid method for the bio-assay of renin has been presented. Reliable and consistent results are obtained by this method whereby an arbitrary dog unit of renin has been established.

The response of normal unanesthetized dogs to renin is independent of the body weight of dogs weighing between 10 and 25 kilograms. An estimate of potency of renin per kilogram of body weight of the test animals is therefore not only unnecessary but misleading.

A dog unit of renin has been defined as that amount which raises the blood pressure at least 30 and not more than 35 mm. Hg within three minutes, in at least three unanesthetized dogs. The potency is expressed as dog units of renin per cubic centimeter.

The determination of the amount of renal substance represented by a cubic centimeter of extract and the number of dog units per cubic centimeter give an estimate of the yield of renin which can be expressed as dog units of renin per gram of original renal tissue.

By determination of the number of dog units per cubic centimeter and the amount of nitrogen in milligrams per cubic centimeter in any renal extract, the purity of the renin can be determined and expressed as dog units of renin per milligram N.

The establishment of a standard method for the bio-assay of renin is considered highly desirable, and the method outlined in this paper is suggested for this purpose.

AUTHORS.

Foa, P. P., Woods, W. W., Peet, M. M., and Foa, N. L.: Effective Renal Blood Flow, Glomerular Filtration Rate and Tubular Excretory Mass in Arterial Hypertension. II. Effect of Supradiaphragmatic Splanchnicectomy With Lower Dorsal Sympathetic Ganglionectomy. *Arch. Int. Med.* 71: 357, 1943.

Diodrast and inulin clearances were used to measure the effective renal blood flow and filtration rate in seventeen patients with arterial hypertension. Measurements were made before bilateral supradiaphragmatic splanchnicectomy with lower dorsal sympathetic ganglionectomy, and from two weeks to twelve months after the operation. The results indicate that the operation did not change the renal blood flow significantly, even when the blood pressure was reduced. There was a reduction of blood pressure in eight patients. Constancy of renal blood flow, combined with reduced blood pressure, suggests decreased vascular resistance and intrarenal arteriolar vasodilatation, with a resultant increase in pulse pressure within the kidney.

The patients with the highest effective renal blood flow, the greatest vasomotility, and the least thickening of the systemic arterioles received the most benefit from the operation. It is suggested that the determination of effective renal blood flow, and the measurement of the wall/lumen ratio of the systemic arterioles in biopsy specimens of muscle, might prove to be valuable in the preoperative study of patients with arterial hypertension.

The authors' results are consistent with the hypothesis that reduced intrarenal pulse pressure, and not renal ischemia, is a causal factor in human hypertension.

AUTHORS.

Pickering, G. W., Prinzmetal, M., and Kelsall, A. R.: The Assay of Renin in Rabbits With Experimental Renal Hypertension. *Clin. Sc.* 4: 401, 1942.

Extracts of rabbit kidneys made by three different methods have been assayed for their renin content by finding the amount raising the unanesthetized rabbit's blood pressure to the same extent as a given dose of a standard preparation. The standard was stable for at least two and one-half years.

The renin content of normal rabbits' kidneys shows considerable variations, the causes of which are undetermined, although higher values tend to occur in rabbits that are immature than in those that are fully grown.

When hypertension is produced by constricting the renal artery in the rabbit, the renin content of the kidney depends on the degree of constriction and on the duration of the hypertension. When the constriction is severe enough to produce renal necrosis, the hypertension is fleeting, and after one to two days the renal renin content is abnormally low. When the constriction is severe enough to produce hypertension within twelve hours, but not to produce renal necrosis, the hypertension is maintained, and in the first eight days the renal renin content tends to be abnormally high. When hypertension has lasted two to seventeen months, the renal renin content is normal.

By a method of extraction described in the text renin can be recovered from blood ten to fifteen minutes after its intravenous injection. None has been recovered from the blood of rabbits with hypertension of two to five months' duration.

The results obtained are consistent with the hypothesis that the hypertension which occurs in the first few days after constricting the renal arteries is due to the release of renin from the kidney. The normal renal content of animals with prolonged hypertension suggests that factors other than the enhanced secretion of renin may contribute materially to the genesis of prolonged hypertension after renal artery constriction. These factors have not yet been identified.

AUTHORS.

Hass, G. M.: Elastic Tissue. III. Relations Between the Structure of the Aging Aorta and the Properties of the Isolated Aortic Elastic Tissue. Arch. Path. 35: 29, 1943.

It is not possible to predict the mechanical or dynamic behavior of isolated elastic networks from knowledge of the behavior of the aortic wall from which they are obtained. The average purified networks are more extensible than the intact aorta. The extensibility is greatest among young networks, and usually increases with age, but occasional aged elastic systems have the characteristic high extensibility of youthful tissue.

The low extensibility of aged dilated intact aortas is partly due to the fact that at zero load the elastic networks are under tension. When the constraints responsible for this constant tension are removed, the elastic networks spontaneously retract to the dimensions of an undilated aorta.

After removal of mechanical or chemical forces, either of which may produce near maximum extension, all purified elastic systems, irrespective of age, exhibit identical and almost perfect retraction.

The tensile strength of isolated networks is, as a rule, high in the early decades, and low in the late decades of life. When elastic systems with low tensile strength are encountered in middle life, peculiar crystal patterns abutted by collagenous splints are found in the axes of elastic lamellae. Elastic systems with low tensile strength in late life have conspicuous discontinuities but not axial crystals. The evidence indicates that some of these discontinuities arise by disintegration of elastic lamellae at focal points of collagenous splinting and axial crystallization. The genesis of these medial changes and their contribution to the formation of atherosclerotic lesions remain obscure.

AUTHOR.

Bartol, G. M., Edwards, J. E., and Lamb, M. E.: Mycotic and Dissecting Aneurysms of the Aorta Complicating Bacterial Endocarditis. Arch. Path. 35: 285, 1943.

The case of a 75-year-old man with acute bacterial endocarditis of the aortic valve, in whom a dissecting aneurysm of the aorta arose in the base of a complicating mycotic aneurysm, is presented.

The etiological organism was a pleomorphic gram-negative lactose-fermenting bacillus that could not be classified accurately.

The case is unusual from several angles, namely, (1) the association of bacterial endocarditis with dissecting aortic aneurysm, (2) the development of dissecting aneurysm in the base of a mycotic aneurysm, and (3) the type of organism responsible for the endocarditis.

AUTHORS.

Bower, L. E., Ditkowsky, S. P., Klien, B. A., and Bronstein, I. P.: Arteriovenous Angioma of Mandible and Retina With Pronounced Hematemesis and Epistaxis. Am. J. Dis. Child. 64: 1023, 1942.

A case is reported of an arteriovenous angioma of the mandible and retina. An obscure cause for spurious hematemesis and epistaxis may be a vascular lesion of the jaw with bleeding around the teeth.

AUTHORS.

out that many drugs are praised in the absence of controlled clinical observations. Thirty-three drugs, in all, were exhibited by them, including nitrites, iodides, bromides, barbiturates, and antispasmodic agents such as atropine and papaverine sulfate. These authors set up certain seemingly fair critical standards for judgment as to whether or not a drug is "hypotensive." Such a drug must reduce the blood pressure when it is originally elevated, must demonstrate this action consistently and in a high proportion of patients, and, last, must do this without producing symptoms of toxicity. In the present study, these have been accepted as suitable criteria for similar adjudication of the drugs concerned. At the conclusion of the aforementioned studies, Evans and Loughnan agreed that they could not approve the prescribing of any of these drugs if the object was to reduce the blood pressure!

PURPOSE OF THE PRESENT STUDY

It was the intention, in the initiation of this study, to assay the actual hypotensive effects of a number of commonly used and widely recommended drugs on patients who had a persistently elevated blood pressure. Because of previous demonstrations that symptomatic improvement is commonly obtained by many methods of treatment,^{7, 19, 20} a careful attempt was made to exclude any consideration of subjective response. As stated before, it is my conviction that the mediator of the high mortality^{3, 14, 17} rate of essential hypertension is the level of intra-arterial pressure itself.

METHODS OF STUDY

Patients.—The patients were selected from a group of persons who were resident in a state hospital for the insane.* This selection was made deliberately, for it was felt that such a group of patients were relatively insensitive to their immediate environment, and all were, perforce, subjected to considerable routine in their daily lives. Also, few, if any, of these patients complained of symptoms of elevated blood pressure, although some were rather ill from the consequences of it. The patients included those who had schizophrenia, manic depressive psychosis, depression, arteriosclerosis of the vessels of the central nervous system, with attending dementia, and some other types of committable mental disturbances. All patients were hypertensive males, with ages ranging from 38 to 70 years. All patients ate the same meals, and each subgroup included those in rather close confinement to the wards, and those allowed more freedom, who carried on simple occupations around the institution. In general, it was a group of patients subjected to much the same environment and routine.

Procedure.—Most of the patients were not told that they were receiving medication, or that they suffered from high blood pressure. A few who exhibited curiosity concerning their pills were told that it was "good for them," and a small number of alert and interested patients were told that they had some slight abnormalities of blood pressure for which they were receiving medication. Last, a small number of institutional employees were treated gratuitously, with full understanding of their abnormal state and the purpose of the study. It was felt that these latter groups would act as controls for evaluation of certain obvious factors.

*We wish to extend our thanks to Dr. B. F. Smith, superintendent, Rochester State Hospital, for his generosity and cooperation in this study.

All persons reported on in this study were subjected to minimal examinations for the purpose of ruling out certain etiological factors which might cause hypertension. Examination of the optic fundi and urinalysis were carried out, and roentgenograms of the thorax were made, in addition to careful physical examination. When observations were made that were suggestive of glomerulonephritis or other significant renal disease, coarctation of the aorta, increased intracranial pressure, or certain endocrine disturbances, including hyperthyroidism, pituitary basophilism, and adrenal tumor,²¹ the patients concerned were omitted from this study. Arteriosclerosis and obesity were not disqualifying for our purposes. Admittedly, some of the aforementioned disturbances may have been present in spite of care taken to exclude them, but it is not likely that the majority of the patients had any cause for elevated blood pressure other than essential hypertension. It was not felt that an abnormal psychic state should be disqualifying, because hypertension is not characteristically observed in the presence of psychoses, and the large majority of the patients of this institution had normal blood pressure. No patient with the clinical or ocular criteria^{3, 22} of "malignant" hypertension was included in this series.

This large group of selected patients was classified into subgroups, referred to by number in Tables I, II, III, IV, V, VI, VII, and VIII. These subgroups were composed of up to ten men, and an attempt was made to include an approximately equal number in each subgroup. Attention was paid to age, occupation, and physical habitus. No deliberate attempt was made to select the subgroups on a basis of the value for the blood pressure or the grouping of the vascular lesion,³ because it was soon apparent that each group was composed of representative patients. Members of each group were given one drug in the dosage recommended by the manufacturer, or other advocate of the product, or in a dosage even exceeding the suggested optimum. The medications were given before meals as a matter of routine. Patients who for reasons of temperament or delusion refused medication for more than one day, or who were detected in attempts to deceive, were eliminated from the study, and new patients were substituted for them. All drugs were ingested by patients under the supervision of experienced attendants. All patients who received other medications independent of this study were omitted from consideration if those medications included sedative agents, iodine-containing substances, digitalis, or other drugs that might affect the blood pressure. Actually, the only other medicines given to these patients during the period of this study included mineral oil, milk of magnesia, insulin (three patients), skin disinfectants, and antipruritic lotions.

Measurements of the blood pressure were made at least three times daily, i.e., before breakfast and lunch, and after supper. With certain few exceptions, all measurements were made by one examiner, and in accordance with the suggestions of the joint British-American Committee²³ for standardization of methods of taking blood pressure. In a few instances in which this was not done, a dispensary attendant, carefully trained according to the aforementioned technique, took the readings. These instances were so few that they did not significantly alter the results. In all cases the daily maximal and minimal systolic and diastolic pressures were recorded, so that in the tables only two daily readings are presented. Among all patients a period of seven to ten days in which medication was not given was devoted to measuring the blood pressure and its fluctuations.

The study period included the seven- to ten-day pretreatment period, and at least thirty days of continuous observation while the patients were under treatment. In almost all cases a further observational period of seven to ten days, after discontinuance of all treatment, was allowed for the detection of any changes in blood pressure that might conceivably occur as "delayed" responses. Thus, it seemed reasonable that within thirty to forty days any hypotensive effects should become manifest.

Certain reasonable criteria had been decided upon, previous to the study, for definition of a hypotensive effect. These had been used by previous investigators.^{12, 18} Prior to, and during, this inquiry a moderately skeptical attitude, rather than an entirely open mind, possessed the author; but perusal of the results will soon demonstrate that any misgivings on this score can be set aside.

DRUGS

The drugs used in this study usually were selected with a view of obtaining at least one representative of each of the currently highly popular types of chemicals used in attempts at regulation of blood pressure. One outstanding omission was potassium thiocyanate, for the technical difficulty of using this drug in such a study is apparent. Furthermore, most authors^{24, 25} are in agreement as to the status of this drug, for many careful and adequate studies of its effects have been made. Some drugs were selected because they had been widely advertised and remarkable claims had been made for them. All drugs used were purchased from ordinary sources.

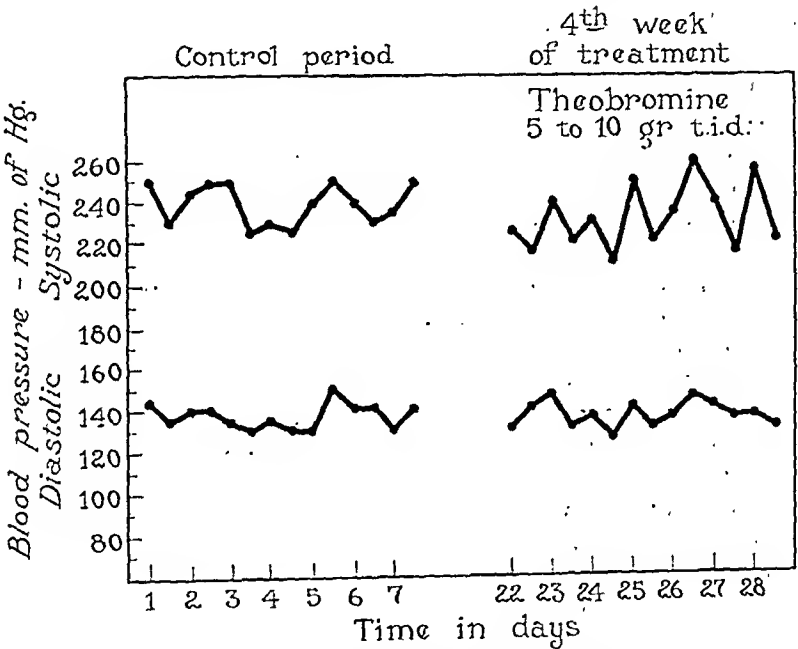


Fig. 1.—Daily values for diastolic and systolic blood pressure in control period and during the fourth week of treatment with theobromine, in a typical case.

TABLE I

RESULTS OF TREATMENT WITH THEOBROMINE, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT				PRESSURES AFTER TREATMENT
		1	2	3	4	
1	182/125	185/130	182/126	175/122	188/126	186/129
2	165/116	165/116	166/112	163/112	159/109	168/113
3	157/111	158/111	165/119	170/121	186/121	179/123
4	239/136	221/134	225/132	226/134	232/136	239/135
5	183/106	170/104	175/108	181/107	178/111	183/112
6	186/117	178/109	175/111	184/114	179/116	180/116
7	179/110	178/102	171/100	168/102	168/ 97	Incomplete
8	203/113	194/115	189/118	188/118	187/121	193/120
9	188/101	187/112	187/110	189/110	184/109	Incomplete
10	212/123	203/120	202/123	206/122	205/122	Incomplete

The methylated xanthine derivatives enjoy widespread favor and, in various forms and combinations, constituted the largest single group of drugs studied. Cushny²⁶ stated that "All members of the caffeine series have been shown in animals to dilate the coronary vessels, but how far these results can be carried over to man is still an open question." In this group, theobromine, a prepared combination of theobromine and phenobarbital sodium (theominal), a proprietary arterial antispasmodic agent (iocapral), and theophylline with ethylene diamine (aminophylline) were tried.

Theobromine.—Theobromine (3, 7 dimethylxanthine) was given three times daily, with meals, in capsules of 5 grains (0.3 Gm.) each. Patients numbered 1 through 10 (Table I) received this drug, and, after two weeks of consecutive use of it, the dose was doubled (Fig. 1); that is, for the second two weeks of consecutive use, the dose was 10 grains (0.65 Gm.) three times daily.

Theobromine and Phenobarbital Sodium.—Theominal, a proprietary drug, was administered to patients numbered 11 through 20 (Table II). This preparation contains, according to the manufacturer's statement, 5 grains (0.3 Gm.) of theobromine

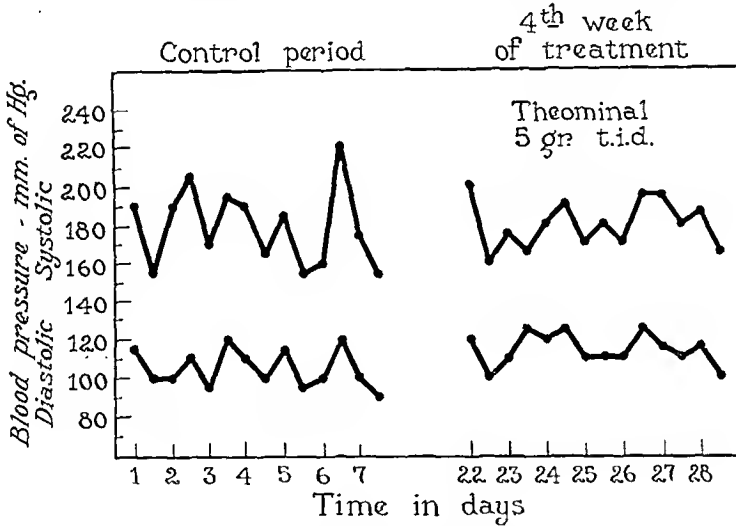


Fig. 2.—Daily values for diastolic and systolic blood pressure in control period and during the fourth week of treatment with theominal, in a typical case.

TABLE II

RESULTS OF TREATMENT WITH THEOMINAL, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT				PRESSURES AFTER TREATMENT
		1	2	3	4	
11	176/115	176/117	176/118	176/115	180/117	185/115
12	180/119	191/125	180/116	174/114	179/119	180/121
13	178/104	165/104	169/104	183/111	177/113	Incomplete
14	191/106	194/116	197/124	196/115	196/124	Incomplete
15	181/100	179/ 99	179/ 98	194/103	Refused further treat- ment	
16	186/114	180/111	186/112	185/114	183/118	Incomplete
17	183/103	202/110	194/112	184/115	Refused further treat- ment	
18	184/108	169/104	168/ 95	175/106	184/109	Incomplete
19	170/ 99	174/101	172/100	172/105	171/104	189/107
20	203/118	192/117	199/118	197/121	Died suddenly	

and a half-grain of phenobarbital sodium (luminal) to the tablet. This was given in the recommended dose of one tablet three times daily. For seven of these ten patients four consecutive weeks of treatment were carried out (Fig. 2), whereas, for three, shorter periods were occasioned by unanticipated events, as set forth in Table II.

Proprietary Arterial Antispasmodic Agent.—Iocapral, also a proprietary remedy, was administered to only five patients for a four-week period (Fig. 3). The patients were numbered 21 through 25 (Table III). This preparation, according to the manufacturer's statement, contains 5 grains (0.3 Gm.) of theobromine, two-thirds of

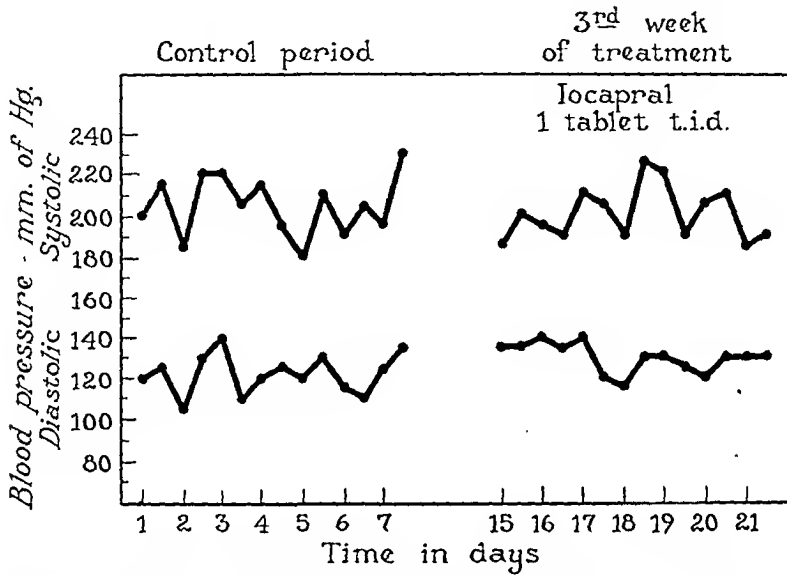


Fig. 3.—Daily values for diastolic and systolic blood pressure in control period and during the third week of treatment with iocapral, in a typical case.

TABLE III

RESULTS OF TREATMENT WITH IOCAPRAL, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT				PRESSURES AFTER TREATMENT
		1	2	3	4	
21	181/116	179/115	187/116	179/122	184/120	185/116
22	174/104	167/104	171/106	169/109	178/108	172/105
23	178/116	182/118	184/119	179/120	183/120	182/117
24	170/118	173/122	170/122	172/119	177/126	177/123
25	205/123	210/135	199/134	199/129	203/125	207/125

TABLE IV

RESULTS OF TREATMENT WITH AMINOPHYLLINE, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT				PRESSURES AFTER TREATMENT
		1	2	3	4	
26	165/101	171/107	180/107	190/113	172/105	181/110
27	224/136	234/135	228/138	229/134	228/136	237/137
28	175/112	169/112	179/115	177/112	173/115	180/119
29	181/111	180/113	180/116	184/117	187/113	194/112
30	205/121	204/125	204/122	202/120	199/123	199/124

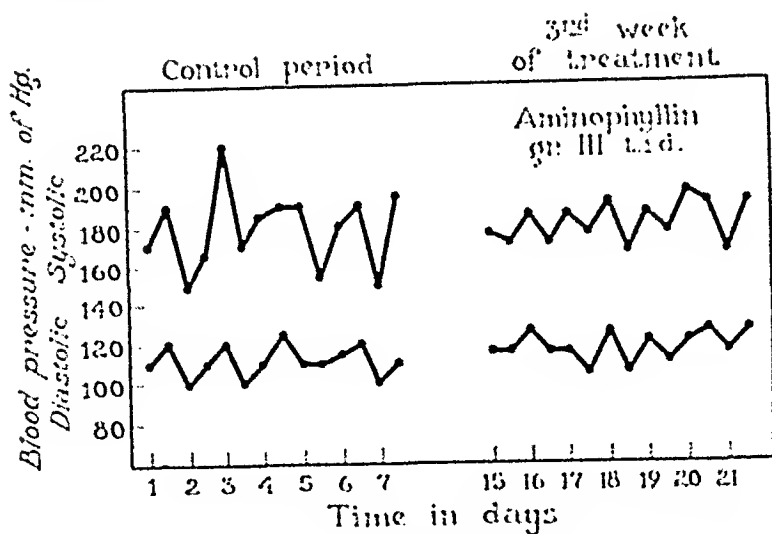


Fig. 4.—Daily values for diastolic and systolic blood pressure in control period and during the third week of treatment with aminophylline, in a typical case.

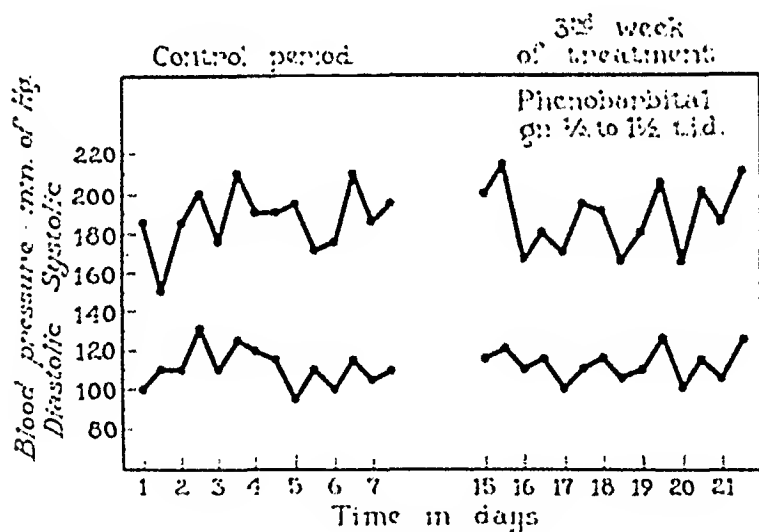


Fig. 5.—Daily values for diastolic and systolic blood pressure in control period and during the third week of treatment with phenobarbital, in a typical case.

TABLE V

RESULTS OF TREATMENT WITH PHENOBARBITAL, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT				PRESSURES AFTER TREATMENT
		1	2	3	4	
31	146/95	144/94	149/98	153/99	149/103	148/104
32	157/102	144/102	152/104	144/96	152/105	146/106
33	184/112	193/115	194/115	189/118	190/119	186/120
34	168/103	157/98	149/93	148/94	141/100	142/104
35	211/96	209/100	208/111	192/108	209/111	215/115
36	186/112	182/110	191/112	185/111	186/113	182/114
37	187/121	180/122	174/122	176/119	181/121	183/122

a grain of mebaral (a brand of mephobarbital, or N-methylethylphenylbarbituric acid), and 2 grains (0.13 Gm.) of calcium iodide ditriethanellamine in each tablet. One tablet was administered three times daily throughout the usual thirty-day period.

Theophylline With Ethylene Diamine.—Aminophylline, a brand of theophylline with ethylene diamine, containing from 70 to 80 per cent of anhydrous theophylline (1,3-dimethylxanthine), was the last of this group of drugs used. This also was administered to five patients, numbered 26 through 30 (Table IV), for the usual period of thirty days, in a dosage of 3 grains (0.2 Gm.) three times daily (Fig. 4).

Phenobarbital.—Phenobarbital, alone, in varying dosages, was given to seven patients for a minimum of four consecutive weeks. These records are numbered 31 through 37 (Table V) (Fig. 5).

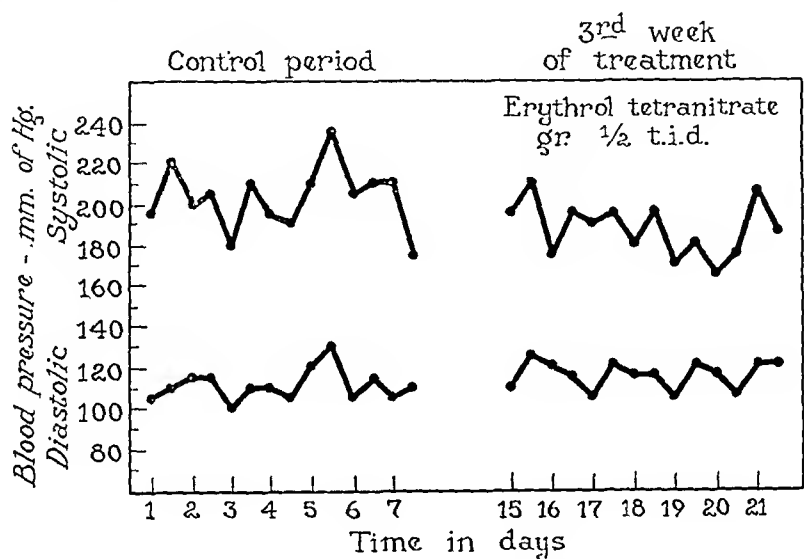


Fig. 6.—Daily values for diastolic and systolic blood pressure in control period and during the third week of treatment with erythrol tetranitrate, in a typical case.

TABLE VI

RESULTS OF TREATMENT WITH ERYTHROL TETRANITRATE, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT				PRESSURES AFTER TREATMENT
		1	2	3	4	
38	202/130	205/129	212/131	199/129	200/130	203/130
39	164/105	161/105	162/107	165/107	164/111	170/110
40	211/111	199/111	206/115	195/116	199/116	189/122
41	167/116	164/110	162/109	174/111	169/110	168/110
42	233/135	239/138	239/138	233/135	240/138	232/140

The nitrites (and nitrates) have been known as vasodilators for many years. Brunton²⁷ wrote, in 1897, that inhalation of amyl nitrite causes “a very great fall of the blood pressure.” Since that time, extensive search has been made for a nitrite or nitrate which would be relatively nontoxic and yet cause prolonged vasodilatation. It was not possible in this study to use all of the organic and inorganic nitrites and nitrates that have been introduced for the management of hypertension. A representative was chosen, after the recommendations of Goodman and Gilman.²⁸

Erythrol Tetranitrate.—Erythrol tetranitrate (C₄H₆[NO₂]₄), the nitration product of erythrol (tetrahydroxybutane), was administered for the usual period in a dosage

of a half-grain (0.032 Gm.) three times daily (Fig. 6) to patients numbered 38 through 42 (Table VI).

A Proprietary Hypotensive Agent.—A proprietary remedy known as hepvisc, of complex and uncertain composition, was administered (Fig. 7) to eleven patients, numbered 43 through 53 (Table VII). Of these eleven patients, nine took this medicine for four weeks and two took it for shorter periods. The scheme of administration, as recommended by the manufacturer, is "one to two tablets three times daily, one-half hour before meals. Best results are obtained when medication is given in courses of two to three weeks, allowing a week's rest interval between courses." This advice was carefully followed. The manufacturer claims that this tablet is "a synergistic combination of *Viscum album* (European Mistletoe), and hepatic and insulin-free pancreatic extracts. It is much to be preferred to the nitrites and other depressing drugs." The advertisements also state that hepvisc is "for prolonged relief of blood pressure." The latter statement seems somewhat ambiguous.

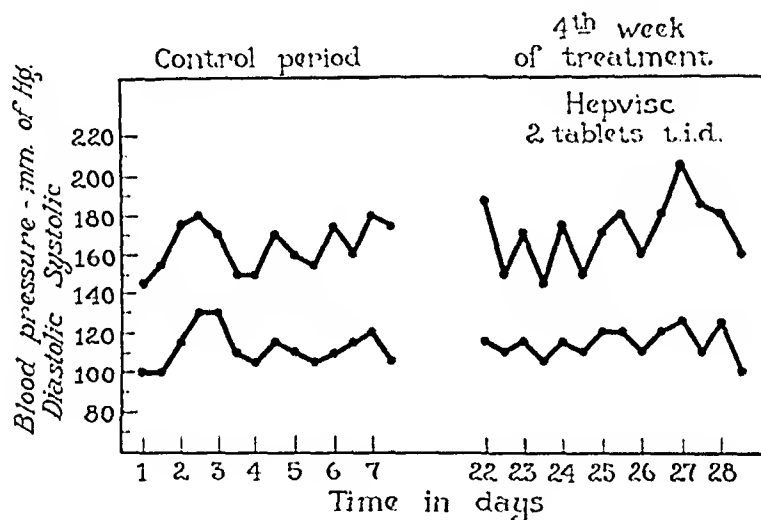


Fig. 7.—Daily values for diastolic and systolic blood pressure in control period and during the fourth week of treatment with hepvisc, in a typical case.

TABLE VII

RESULTS OF TREATMENT WITH HEPVISC, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT				PRESSURES AFTER TREATMENT
		1	2	3	4	
43	164/112	160/109	163/114	160/111	174/114	165/113
44	166/103	156/99	157/101	158/103	166/109	161/105
45	198/118	202/116	220/124	216/120	Fractured hip; bronchopneumonia	
46	165/106	172/116	169/109	167/106	167/108	159/103
47	158/105	158/101	161/104	168/110	165/108	164/106
48	215/137	204/131	190/128*	180/121*	184/119*	185/120*
49	184/125	175/123	178/121	178/121	183/125	178/123
50	166/111	188/118	183/119	187/119	188/121	180/120
51	142/100	143/96	148/101	145/100	145/99	146/100
52	185/118	188/120	192/126	191/121	197/120	191/124
53	184/109	184/109	190/113	181/110	189/111	189/117

*Rest in bed.

A Proprietary Vasodilator.—Another proprietary remedy, known as allimin, has been widely circulated among the profession. It was given (Fig. 8) to ten patients (54 to 63) for four consecutive weeks (Table VIII). This preparation is stated to be "a synergized combination, each tablet containing four and three-fourths grain garlic concentrate and two and three-eighths grain parsley concentrate with excipients and coating." Physicians are directed to give (average dose) two tablets with water, three times daily after meals for three consecutive days, omitting its use on the fourth day, and repeating this procedure indefinitely. The active principle, if any, would seem to be allyl sulfide (oil of garlic). This remedy is said by the manufacturer to produce a "systolic and diastolic drop in hypertensives," demonstrated clinically. It is also claimed to have "an antiputrefactive action in the gut—a significant collateral action in many cases of hypertension." The latter is a statement that seems hardly justified.

This list of drugs is not an imposing one when it is considered that more than 100 drugs are currently recommended as "hypotensive" agents.⁶ However, the list includes representatives of many large groups of drugs which are chemically related.

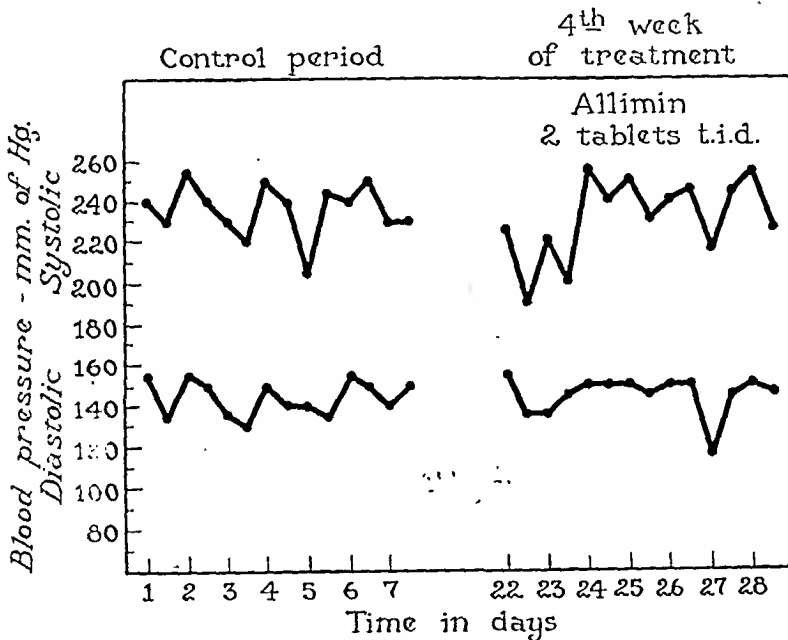


Fig. 8.—Daily values for diastolic and systolic blood pressure in control period and during the fourth week of treatment with allimin, in a typical case.

TABLE VIII

RESULTS OF TREATMENT WITH ALLIMIN, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT				PRESSURES AFTER TREATMENT
		1	2	3	4	
54	237/142	227/143	226/144	221/147	237/145	228/142
55	169/106	171/106	185/118	185/114	186/117	180/110
56	238/135	238/133	242/134	243/132	248/138	239/136
57	157/ 93	156/ 99	163/ 96	162/ 96	158/ 99	161/ 98
58	206/101	204/ 99	220/104	215/105	223/104	218/102
59	173/ 98	155/ 92	170/110	177/105	174/102	169/101
60	191/121	186/121	196/118	201/122	203/130	194/121
61	210/120	201/116	204/122	209/122	207/121	206/119
62	199/123	191/119	204/121	192/121	194/125	193/126
63	178/114	172/114	178/115	180/120	186/119	184/120

RESULTS

The results of this study, to even the most optimistic observer, are uniformly disappointing. In no single case was a sustained, significant¹² reduction in blood pressure seen. The appended tables, in which blood pressures are recorded as taken, bear evidence that no drug among those studied had any hypotensive effect when it was administered in the stated dosage for long periods. It is not likely, in view of the experiences of others,^{7, 17, 18} plus the information gained in this study, that any of the groups of drugs represented by the selected examples referred to herein are likely to be any more effective.

CONCLUSIONS

On the basis of this study, it may be reasonably concluded that certain drugs, meaning those referred to herein and others similar to them, when administered continuously in optimal dosage for periods of thirty days, do not possess any significant hypotensive effect upon the blood pressure of hypertensive patients. Furthermore, the observer is strongly inclined to question the effectiveness of chemically similar drugs, of which the chosen preparations may be considered representative samples.

The author agrees with other workers¹⁸ that the prescribing of these drugs is not to be recommended if the purpose of such prescription is to reduce the blood pressure of hypertensive patients.

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THE NORMAL BLOOD PRESSURE IN THE LOWER EXTREMITY

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INTRODUCTION

THE auscultatory (indirect) method of estimating arterial blood pressure in the arms is widely employed. Normal standards, based on figures obtained with this technique in large numbers of subjects, are already well established. So far as the authors are aware, however, similar data for the lower extremities of man are not yet available, even though the blood pressure in the thigh has been the subject of attention in cases of aortic insufficiency and coarctation of the aorta. The purpose of this preliminary report is an attempt, from a study of 500 normal soldiers, to supply this information, due consideration being given to certain modifying factors.

METHOD

The subjects used in this study were members of the United States Army Air Forces; therefore, only males were included. Their ages ranged from 18 to 35 years. They were presumed to have normal cardiovascular systems, as judged by physical, fluoroscopic, and ophthalmoscopic examination. No special selection was attempted, other than to exclude those whose blood pressure in the arm exceeded 140 mm. of Hg, systolic, or 90 mm., diastolic, or whose heart rate was over 90 beats per minute. The subjects assembled in a quiet, warm ward and remained unclothed in the supine position for at least thirty minutes prior to the measurement of the arterial blood pressure. External disturbing stimuli, apprehensiveness, and chilling were eliminated as much as possible. The environment was kept quiet, restful, and conducive to complete relaxation, as evidenced by the fact that many soldiers fell asleep. During this rest period the eye grounds and heart were examined and the temperature was taken orally. The circumference of the arm midway between the shoulder and elbow, and that of the thigh, four inches above the upper edge of the patella, were then measured by a steel tape. After the men rested for one-half hour, the pulse rate and blood pressure were recorded. The height and weight with the subjects unclothed were obtained at the conclusion of the session.

The technique and precautions recommended by the American Heart Association¹ for the estimation of the arterial blood pressure were followed with certain exceptions. As suggested, the diastolic level in the arm was recorded at the beginning of the fourth phase (muffling of the Korotkov sounds); however, in the lower extremity, since the fourth phase is inconstant, the diastolic pressure was considered to correspond

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to the point at which the sounds were no longer audible.* Also, it was found more expedient to measure the pressure in the thigh with the subject in the supine, rather than in the prone, position. One other deviation from the recommended procedure was the use of a standard-width cuff in the lower extremity instead of a wider cuff. In the arm, the bag portion of the cuff was placed over the brachial artery with the lower edge about one inch above the antecubital space, whereas, in the thigh, it was placed over the popliteal artery with the midportion of the cuff four inches above the upper edge of the patella. The blood pressure was estimated by the authors as simultaneously as possible in homolateral extremities, care being taken that the limbs were relaxed, extended, and approximately at heart level. The average of three closely agreeing measurements (one of which was checked by both observers),† taken successively and interrupted by complete deflation of the cuff, was the figure used in this study.

APPARATUS

Two standard aneroid sphygmomanometers, which were checked against each other and against a mercury manometer, were used in this study. Standard-sized cuffs, 22 inches (55.9 cm.) in length, containing a rubber bag $5\frac{1}{2}$ inches (14 cm.) in width and 9 inches (22.9 cm.) in length, were employed. The cuffs were fitted with metal ribs and a locking device which prevented bulging or slipping of the inflated portion of the bag. This was particularly useful for the successful application of the cuff to the thigh. Occasionally, a thigh was too large to be inclosed in the standard-length cuff, in which case a longer cuff, measuring 29 inches (73.7 cm.) in length, was necessary.‡ The size of the rubber bag in this longer cuff was the same as that in the standard one. For auscultating the Korotkov sounds, ordinary stethoscopes with diaphragm-type chest pieces of approximately the same size were used in both the antecubital and popliteal spaces.

RESULTS

Blood Pressure Range.—In normal adult males between the ages of 18 and 35 years, the blood pressure in the lower part of the thigh, as measured at rest by the standard auscultatory method, ranged from 110 mm. to 230 mm. of Hg (average, 154.8 mm.) systolic, and from 60 mm. to 150 mm. (average, 91.9 mm.), diastolic. The blood pressure in the arm for the same group varied from 90 mm. to 140 mm., systolic, and 50 mm. to 90 mm., diastolic, with an average of 118.3 mm. and 70.6 mm., respectively. The difference between the average arm and thigh blood pressures was 36.5 mm., systolic, and 21.4 mm., diastolic. The average pulse pressure in the thigh was 62.9 mm., and, in the arm, 47.7 mm. In all cases the systolic pressure in the thigh exceeded the corresponding pressure in the arm. The diastolic pressure in the thigh either equalled or exceeded that in the arm; in no instance was it less.

*The auditory perception of the authors was checked with an audiometer, and it was found in both instances to be normal in the frequency range from 128 to 9,747 cycles per minute.

†Shoek and Ogden² have shown by statistical analysis that such a procedure reduces any significant error to a minimum.

‡A cuff with an extension to fit exceptionally large thighs was supplied through the courtesy of the Taylor Instrument Company, Rochester, New York.

The pulse pressure in the thigh in different subjects with similar systolic pressures was rarely identical. No consistent quantitative correlation existed between the systolic and diastolic levels in the arm and the thigh.

Fig. 1 shows that the most frequent (31.2 per cent) systolic pressure readings in the thigh were between 140 and 150 mm. of Hg. In 454 soldiers (90.8 per cent) the range was from 125 mm. to 180 mm. The most frequent (35.8 per cent) diastolic pressure readings in the thigh were between 85 mm. and 90 mm. Hg. In 444 soldiers (88.8 per cent) the range was from 75 mm. to 110 mm.

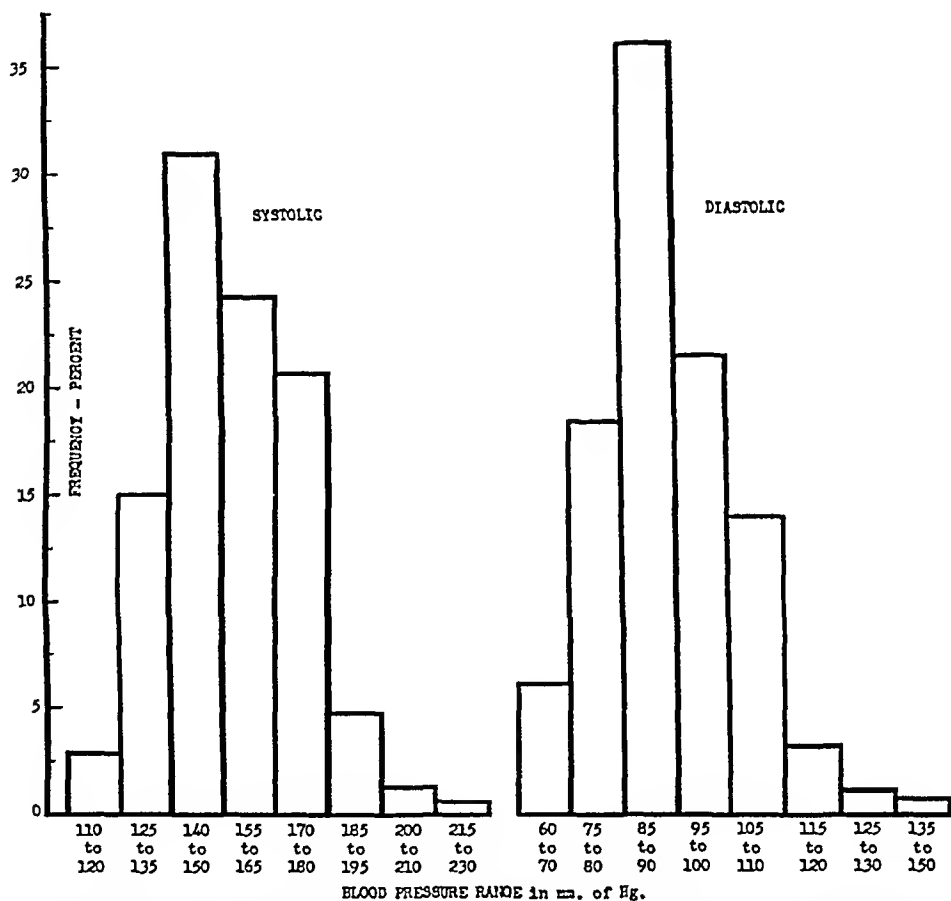


Fig. 1.—The frequency distribution of systolic and diastolic blood pressure readings obtained from the thighs of 500 normal soldiers by the auscultatory (indirect) method.

Height.—Within this group, height (66 to 78 inches) did not significantly influence the average systolic and diastolic blood pressure in the thigh.

Age.—Although age does not appear to be a modifying factor, the limited age range in this group (18 to 35 years) does not warrant any conclusions.

Sex.—Inasmuch as only male subjects were employed in this study, the influence of sex cannot be stated.

TABLE I

RELATIONSHIP OF INCREASING PULSE RATES TO AVERAGE BLOOD PRESSURE IN THE ARM AND THIGH
(The Figures in Parentheses Indicate the Range of Pressure)

PULSE RATE PER MINUTE	THIGH SYSTOLIC (MM. HG)	THIGH DIASTOLIC (MM. HG)	ARM SYSTOLIC (MM. HG)	ARM DIASTOLIC (MM. HG)	NUMBER OF CASES
51-60	151.5 (120-190)	90.5 (70-130)	115 (90-140)	70 (60-90)	62
61-70	154.1 (110-220)	92 (60-140)	115.6 (90-140)	70.8 (55-90)	151
71-80	155 (110-210)	91.7 (60-150)	118.6 (95-140)	70 (50-90)	211
81-90	159.6 (125-220)	93 (75-125)	124 (100-140)	72.7 (55-90)	76

TABLE II

RELATIONSHIP OF WEIGHT TO AVERAGE BLOOD PRESSURE IN THE ARM AND THIGH
(The Figures in Parentheses Indicate the Range of Pressure)

WEIGHT IN POUNDS	THIGH SYSTOLIC (MM. HG)	THIGH DIASTOLIC (MM. HG)	ARM SYSTOLIC (MM. HG)	ARM DIASTOLIC (MM. HG)	NUMBER OF CASES
100-140	145.4 (110-185)	85.8 (60-115)	114.8 (90-140)	69.7 (50-85)	117
141-160	150.9 (110-210)	89.6 (60-130)	116.9 (90-140)	69.4 (50-90)	190
161-180	161.5 (130-205)	96.9 (80-150)	120.9 (100-140)	71.0 (55-85)	138
181-220	169.2 (115-230)	103.7 (75-140)	121.4 (100-140)	73.0 (50-90)	55

Pulse Rate.—Table I shows that, in the pulse range from 51 to 90 beats per minute, there was a slight influence of pulse rate upon the level of the average systolic, but not upon the average diastolic, pressure. With the faster pulse rates, the systolic pressure in both the arm and thigh tended to be higher, and the greater change in this direction was in the thigh. These figures are not statistically significant.

Weight.—Table II shows that, in the weight range from 100 to 220 pounds, there was a direct relationship between the weight of the subject and the height of the systolic and diastolic pressure. This correlation existed in both the arm and the thigh, but in the lower extremity the increase in blood pressure with increase in weight was more evident. The statistical stability test shows that the sampling is adequate except for those who weighed from 181 to 220 pounds.

Circumference of Extremity.—Fig. 2, plotted from the average systolic and diastolic blood pressure readings in both the upper and lower extremities, shows, in general, that the pressure increment in the heavier subjects is dependent on the thickness of the limb. This is most evident in the highest circumference ranges of the thigh. In limbs with similar degrees of soft tissue mass (about 13 inches in circumference), the pressure in the thigh was higher by 25 mm., systolic, and 15 mm., diastolic, than in the arm.

Fig. 3 shows that the greater the average difference in circumference between the thigh and arm, the greater is the average difference between the thigh and arm blood pressure, both systolic and diastolic. The pulse rate values are almost identical in each group, which excludes tachycardia as a causative factor.

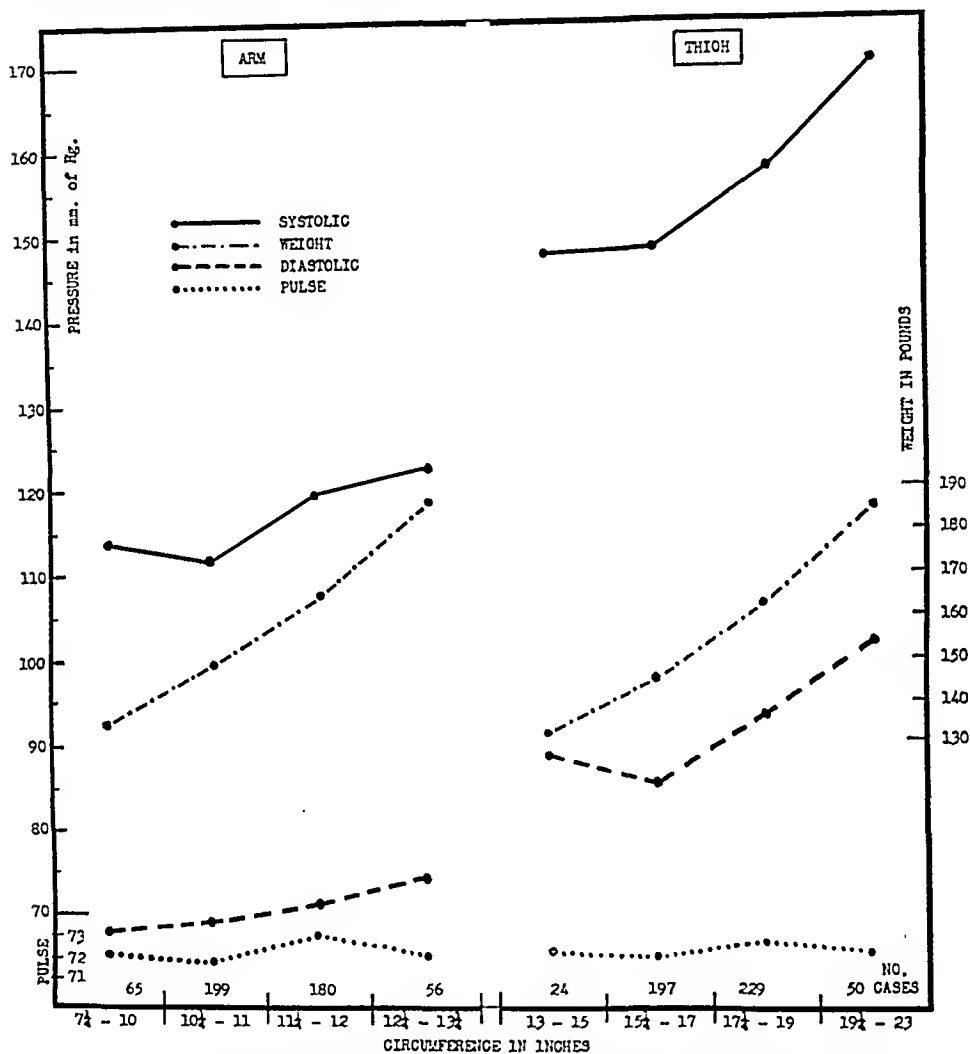


Fig. 2.—The relationship of blood pressure and weight to the circumference of the arm and thigh. The average pulse rate is also shown.

DISCUSSION

Physiologically, the height of the systolic blood pressure in the aorta and its tributaries is dependent on various factors. One of these is the conversion into lateral pressure of the kinetic energy* derived from each systolic discharge of the left ventricle. Since kinetic energy is represented by one-half of the product of the mass and the square of the velocity, the longer the blood vessel (within certain limits), the

*Bernoulli's theorem states that, except for loss by friction, the sum of the potential energy, pressure energy, and kinetic energy will always remain constant.

greater the blood mass, and, presumably, the greater the kinetic energy. This transformation of kinetic energy may be unequal in the various portions of the arterial tree, and, as has been suggested, would be greater in the femoral and popliteal vessels than in other arteries because the former represent an almost direct continuation of the large system consisting of the aorta and common iliaes with their large mass of blood.³

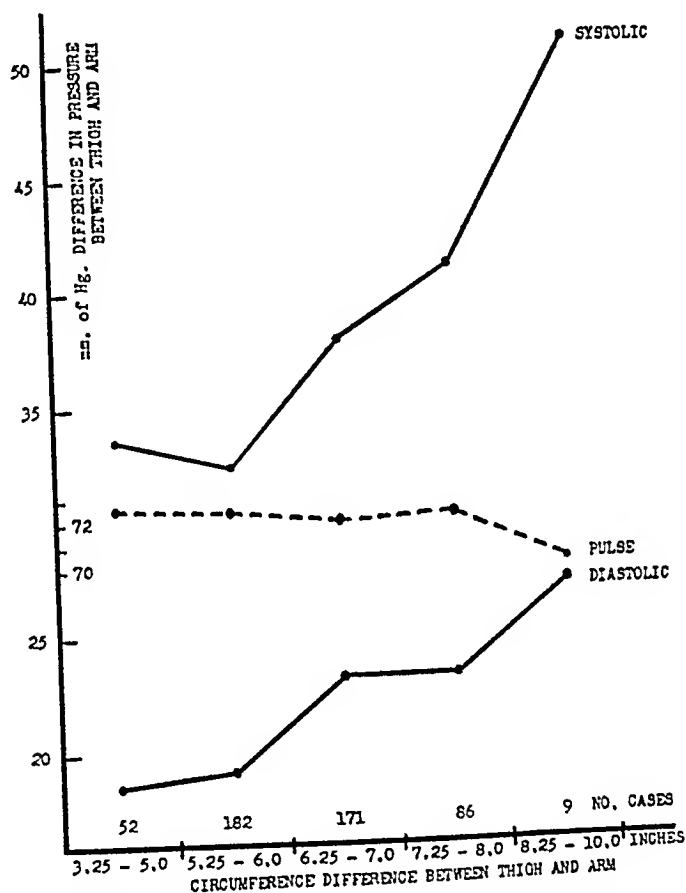


Fig. 3.—The relationship of the circumference difference to the blood pressure difference between the arm and thigh. The average pulse rate is also shown.

Hamilton and Dow¹⁶ studied arterial pressure curves taken at different distances from the aortic arch in dogs. They showed that the peak systolic pressure increases progressively in passing down the aortic-femoral system. This they attribute to the superposition of a standing reflected wave, presumably arising from leg vessels near the knee. Thus, with the subject in the horizontal position to eliminate hydrostatic effects, it is to be expected that the systolic pressure in the thigh will exceed that in the arm. This view is supported by the observations of Burdick, et al.,⁵ who employed a special photographic recording device for registration of the blood pressure in five normal adults, and concluded that the systolic pressure in the thigh is constantly higher than in the arm, and that the difference is commonly 20 to 40 mm. Hg. The present study, based on blood pressure estimations with the standard

auscultatory method on 500 normal men, indicates that, in the thigh, the average systolic and diastolic pressures are, respectively, 36.5 mm. and 21.3 mm. higher than in the arm. Therefore, the statement of Norris, et al.,⁴ that "under normal conditions the systolic pressures in the arm and leg of an individual lying quietly in a horizontal position are equal" seems to be erroneous.

The weight of the subject apparently exerts a modifying influence upon the blood pressure, for higher pressures are present in the heavier subjects (Table II, Fig. 2). This observation is in agreement with the data accumulated by various investigators⁶⁻¹⁰ concerning the relationship of obesity to the brachial blood pressure. This suggests that the soft tissue mass in a limb may, for technical reasons, affect the estimation of the blood pressure. Although others have arrived at such a conclusion by comparing the blood pressure estimations in an atrophied arm and its normal mate,^{11, 12} by a comparison of intra-arterial and indirect measurements of the pressure in the same limb simultaneously,^{13, 14} and by a theoretical consideration of the compressing properties of an inflated pneumatic cuff around a heavy arm,¹⁵ none has attempted to prove this in a large series by correlating the blood pressure in a limb with the circumference. It will be seen from this study (Figs. 2 and 3) that a direct relationship exists between the circumference of the upper and lower limbs and the blood pressures as measured in them by the auscultatory method. This correlation is not invalidated by the fact that, in similar circumference groups (about 13 inches), the average systolic pressure in the thigh is about 25 mm. higher than that in the homolateral arm (Fig. 2), for this is a normal difference.⁵ No quantitative relationship between the thigh and arm pressure can be established at this time. However, with data from a larger series of cases, it might be possible to predict the normal blood pressure in the thigh from a knowledge of the arm blood pressure and circumference of the arm and thigh.

To reduce to a minimum the number of variables in this study, the blood pressures in the arm and thigh were measured with a standard-width cuff, even though it is recommended¹ that, in the lower extremity, a cuff containing a rubber bag 2 cm. wider than the standard be employed. This exception was taken for other reasons: (1) The construction of the cuff used in this study prevented slipping and bulging on heavy, tapered limbs, even when it was inflated, and therefore seemed to eliminate the need for a cuff 2 cm. wider; (2) the work of Ragan and Bordley¹⁴ indicates that, in subjects with heavy limbs, if an extra-wide cuff fitted with a locking device to prevent bulging or slipping is employed, the blood pressure readings are frequently too low as compared with direct intra-arterial measurements; and (3) it is desirable to establish normal standards, based on the use of a stand-

ard-width cuff, so that routine estimation of the blood pressure in the thigh is rendered more practicable; a special-sized cuff would defeat this purpose.

SUMMARY

1. Employing the standard auscultatory method for measuring blood pressure, average values for the lower extremities of 500 normal male subjects were obtained.

2. The average arterial pressure in the thigh, with the subject in the horizontal position, is 154.8 mm. Hg, systolic, and 91.9 mm., diastolic, and, in the arm, 118.3 mm., and 70.6 mm., respectively.

3. The influence of soft tissue mass on the blood pressure estimation is discussed. Evidence is presented to support the thesis that the higher arm and thigh pressures recorded in heavy subjects by the indirect method are probably influenced in part by the thickness of the limb.

4. No equipment other than that ordinarily employed for estimating the pressure in the arm was used for the thigh.

The authors wish to thank Robert E. Shilling, First Lieutenant, A.C., who assisted with the statistical analysis.

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A COMPARISON OF THE ACTIONS OF FOUR CARDIAC GLYCOSIDES ON A PATIENT WITH CONGESTIVE HEART FAILURE

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IN THE course of studies dealing with the circulatory effects of the cardiac glycosides, we encountered a patient on whom a series of observations were made which to us seemed of particular interest.

The several cardiac glycosides are known to show differences in their action.¹⁻⁵ A full knowledge of these differences requires that many components of the circulation be examined (simultaneously, if possible) during the action of the glycosides on patients with congestive heart failure. Ideally, the circulation should be studied in the same patient when therapeutic doses of the different glycosides are given successively in equal gram-molecular amounts during like degrees of circulatory failure. Such a situation is rarely attained. As a rule, the circulation compensates partially or completely after the administration of the first glycoside, and this renders a comparable state for further observations impossible. In the present case, congestive circulatory failure returned to relatively the same status after the temporary improvement produced by each of a series of glycosides. It was then possible to compare the glycosides under conditions simulating the ideal. This comparison is here reported.

In studying the effects of drugs on congestive heart failure, the cardiac glycosides present certain advantages over digitalis leaf. Preparations of digitalis have the disadvantage of unknown and variable composition.⁶ The glycosides are available in pure crystalline form and their chemical structure is known. The complete glycoside consists of a sterol nucleus to which is attached at carbon 17 a butyrolactone ring, at carbon 3 a desoxy-sugar, and, to the desoxy-sugar, several monosaccharide units may be attached.⁷

In this study, four glycosides were employed: lanatoside C, digoxin, digitoxin, and ouabain. Of these, only lanatoside C has all of the component structures outlined above. On hydrolysis, lanatoside C yields digoxin plus a monosaccharide (in this instance glucose) and acetic acid.^{6, 7} By similar hydrolysis, digitoxin is derived from lanatoside A or purified glycoside A, and ouabain (strophanthin) from *strophanthus gratus*. By employing these four purified substances, we were pre-

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pared to compare a structurally complete glycoside (lanatoside C) with its first hydrolysis product (digoxin), and that product with similarly derived hydrolysis products (digitoxin, ouabain) of other structurally complete glycosides.

METHODS

All of the observations were made on the same patient, a 48-year-old woman with moderately severe congestive heart failure. The cause of her heart disease remained uncertain, but it was considered to be of the rheumatic type. There were no valvular defects. The rhythm was uncontrolled auricular fibrillation, with a rapid ventricular rate.

The patient was given, successively, several cardiac glycosides,* administered in equal gram-molecular amounts, as follows: lanatoside C, 0.63 mg.; digoxin, 0.5 mg.; digitoxin, 0.5 mg.; and ouabain, 0.375 mg. This amounts to the administration of equal numbers of molecules of each drug, and permits a comparison of the glycosides in terms of molecule for molecule. The digitoxin was administered as digitaline Nativelle, a commercial preparation which is considered to contain at least 90 per cent crystalline digitoxin. The only other medication received by the patient throughout the study consisted of laxatives and mild sedatives.

The glycosides were always given intravenously. This was done for two reasons: (1) to eliminate differences in absorption of the drugs, and (2) to induce therapeutic effects quickly (within several hours). When the heart failure is relieved partially or completely within several hours, observations can be made continuously throughout the entire period of recovery. This permits primary effects to be readily recognized and differentiated from secondary effects. Such a differentiation is not always possible when observations are made at intervals of many hours or days.

The glycosides were given only when the patient had congestive heart failure. Each glycoside induced a prompt therapeutic effect which persisted for several days, after which heart failure reappeared. Another glycoside was then administered. It cannot be maintained that the degree of congestive circulatory failure was *exactly* similar each time a glycoside was given, particularly because the decompensation seemed to become more severe toward the close of the study. However, by giving each drug (except lanatoside C) twice, and the second dose during a somewhat different state of the circulation, it was possible to compare the different glycosides at quite similar degrees of congestive circulatory failure.

Before a glycoside was given, the patient showed certain subjective and objective signs which indicated that the circulation had lapsed into relatively comparable states of failure. These were complaints of dyspnea, nervousness, restlessness, sweating, and precordial discomfort; a ventricular rate of 150 per minute, or more, for at least two days, usually three; and elevation of the venous pressure to 140 mm. to 150 mm. of saline. Usually five days elapsed between the successive injections of the glycosides. Once eight days elapsed before the above criteria were present. The last glycoside was given after an interval of but three days. The patient had suddenly developed cerebral infarction;

*The authors wish to thank the following companies for generous supplies of the drugs used in this study: Burroughs Wellcome and Company, Inc. (digoxin); Carroll Dunham Smith Pharmacal Company (ouabain); Labatoire Nativelle, Paris (digitaline Nativelle); Sandoz Chemical Works, Inc. (lanatoside C).

digitalis was considered immediately necessary, and the above criteria were discarded.

A number of components of the circulation were measured frequently, and often simultaneously, before and during the action of each glycoside. The ventricular rate was counted, always for a full minute, by auscultation over the precordium. The arterial blood pressure was measured

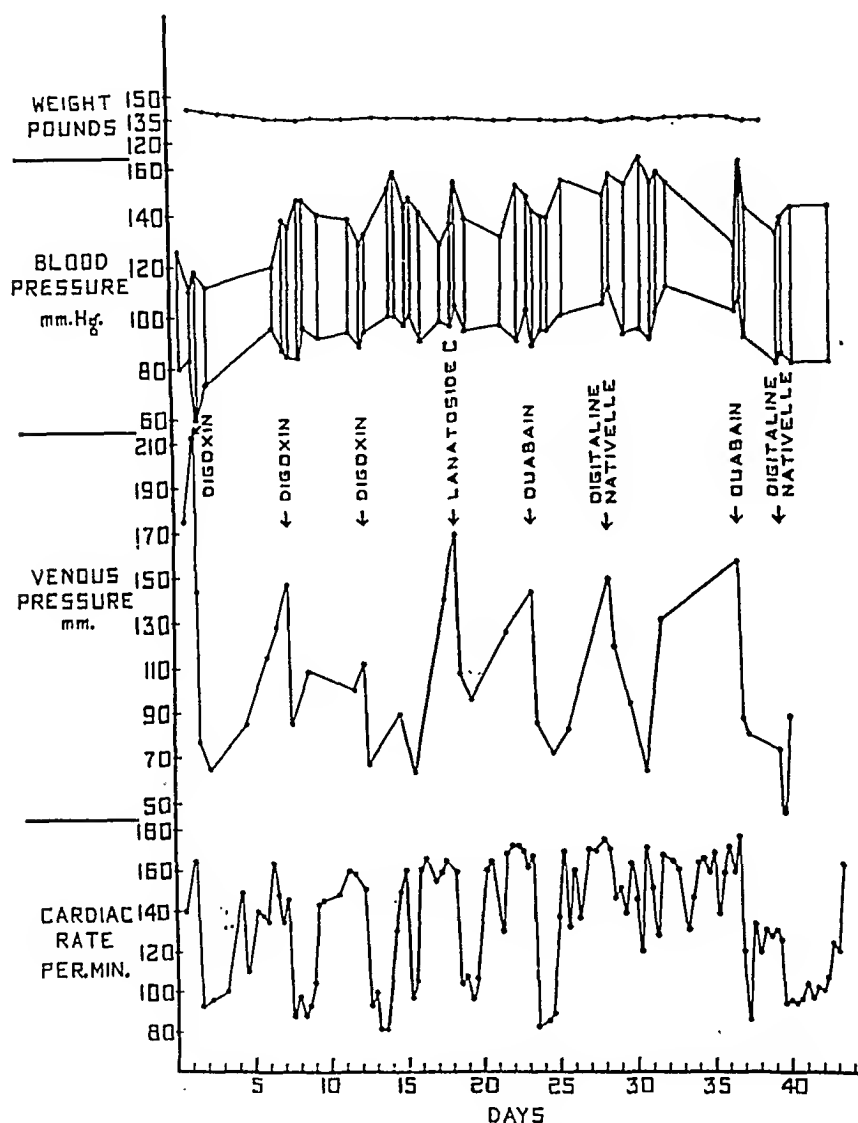


Fig. 1.—General course of several circulatory components throughout the study. Excepting the first dose of digoxin (1.5 mg.), the glycosides were given in equal gram-molecular doses: digoxin, 0.5 mg., lanatoside C, 0.63 mg., ouabain, 0.375 mg., and digitaline Nativelle, 0.5 mg.

by the usual auscultatory method (with mercury manometer). Electrocardiograms were obtained by standard limb leads. Venous pressure was measured in the antecubital veins by the direct method, using a saline manometer. The vein and manometer were always levelled at the same point, namely, 5.5 cm. posterior to the angle of Louis. Respiration was registered by a pneumograph encircling the chest. The volume of blood flow to the hand and calf (two dissimilar vascular areas) was

measured simultaneously by the plethysmographic method. The volume blood flow was measured during resting conditions and during the reactive hyperemia immediately after a five-minute period of ischemia. Teleoroentgenograms and roentgenkymograms were made two to three hours before the injection of a glycoside, and again three to four hours after injection, when therapeutic effects were established. After decided slowing of the ventricular rate had occurred, vagal influence was abolished by the intravenous injection of 2.0 mg. of atropine sulfate, usually given one and one-half to two hours after the administration of the glycoside.

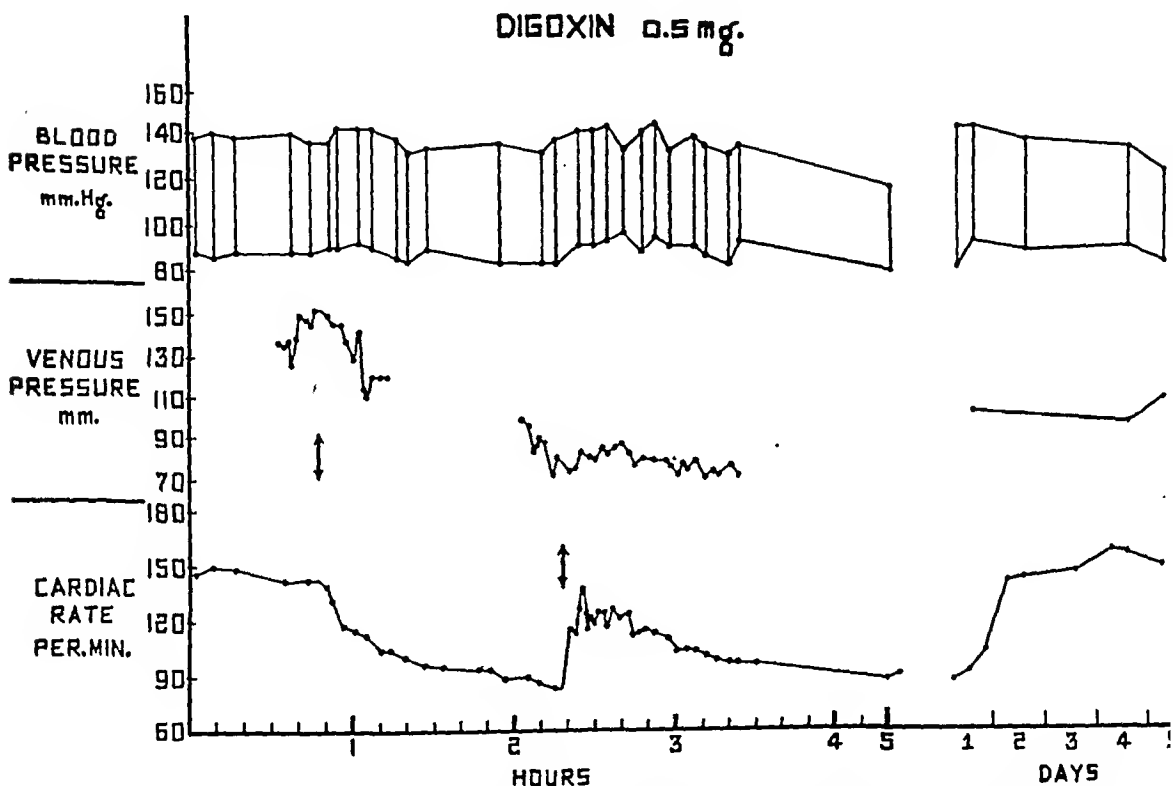


Fig. 2.—Circulatory effects induced by 0.5 mg. digoxin administered intravenously. Degree of decompensation moderate. In this and subsequent charts the following obtains: The data of each chart are from the control period before injection of a glycoside to and including the control period before the next glycoside. The first vertical double arrow indicates injection of the glycoside, the second arrow injection of atropine sulfate.

The observations were made in the morning, with the patient in a fasting state. One study (the second injection of ouabain) was carried out in the evening, when the sudden occurrence of more severe heart failure demanded immediate treatment.

RESULTS

The course of several circulatory components throughout the period of study is presented in Fig. 1, which shows the comparative effects produced by the four glycosides. The ventricular rate generally remained at 150 to 160 per minute. After each glycoside the rate fell sharply to normal, where it remained for several days. It then rose quickly to its previous high level. An abrupt fall of the venous pressure to normal

and a slight increase in the arterial pulse pressure accompanied each decrease in ventricular rate. The venous pressure tended to return to its former high level more slowly than the ventricular rate. The changes in ventricular rate and venous pressure were relatively short-lived, and their duration was comparable when digoxin, lanatoside C, and ouabain were given. When digitaline Nativelle induced similar changes, they were slower in their onset and longer in duration (Tables I and II).

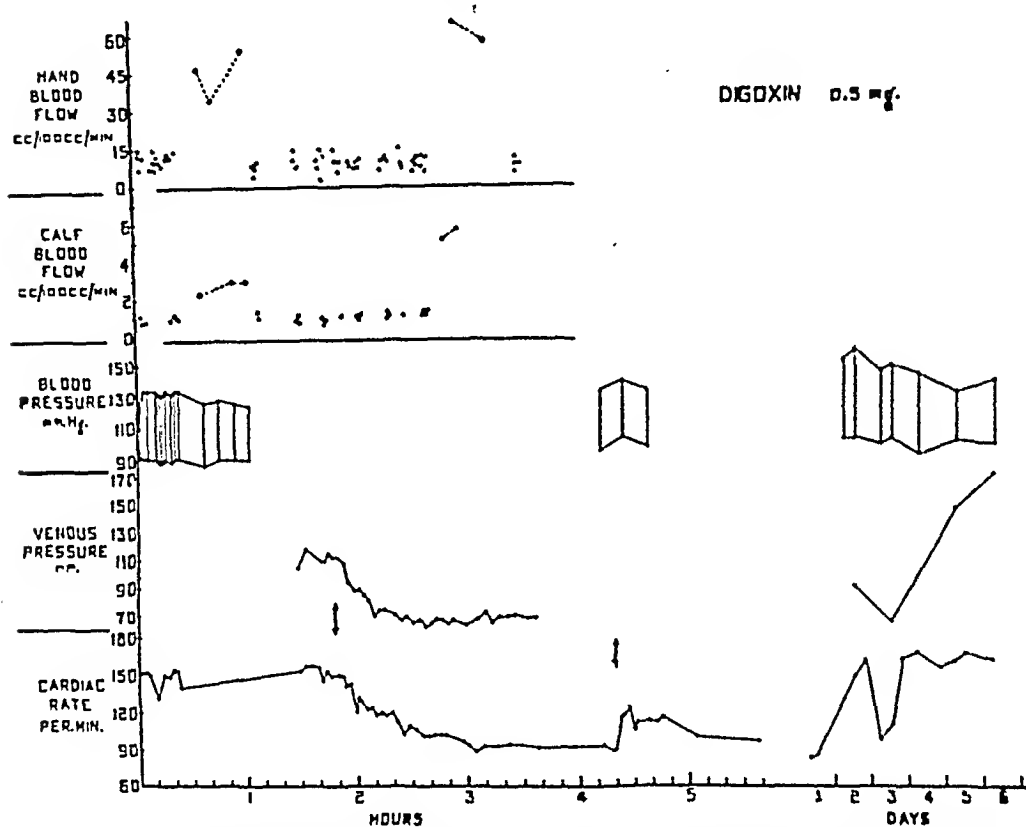


Fig. 3.—Circulatory effects induced by 0.5 mg. digoxin administered intravenously. Degree of decompensation moderate. In this and subsequent charts the volume of blood flow to the hand and calf during the resting state is indicated by the unconnected solid dots; blood flows during reactive hyperemia are connected by the dotted lines. Each dot represents a measurement of blood flow.

Each subsequent chart (Figs. 2 to 8) shows the effects produced by a glycoside from the time of its injection until the next drug was given. The charts are presented in the order in which the drugs were administered. The effect of the first dose of digoxin is not graphed because the amount (1.5 mg.) given exceeded the calculated, equal, gram-molecular dose. Rather than analyze the charts in detail, the circulatory effects of the glycosides will be indicated in relative terms.

Ventricular Rate (Table I).—Onabain decreased the ventricular rate most rapidly; initial slowing was noted within three to four minutes (Figs. 5 and 7). Several hours elapsed before significant slowing occurred after digitaline Nativelle (Figs. 6 and 8), and the full effect was

TABLE I
EFFECT OF THE CARDIAC GLYCOSIDES ON THE VENTRICULAR RATE

DATE	GLYCOSIDE	DOSE IN MG.	CONTROL* VEN- TRICULAR RATE PER MINUTE	ONSET OF VEN- TRICULAR SLOWING MINUTES	PERCENTAGE DECREASE IN VENTRICULAR RATE BELOW CONTROL VALUE: TIME AFTER INJECTION OF GLYCOSIDE																			
					10 MIN.		20 MIN.		30 MIN.		1 HOUR		2 HOURS		1 DAY		2 DAYS		3 DAYS		4 DAYS		5 DAYS	
					MIN.	MIN.	MIN.	MIN.	HOUR	HOURS	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
12/23/41	Digoxin	1.5	160-185 (165)	4-8	15.2	28.4	37.6	40.5	43.6	41.2					39.4		21.2	35.8	15.1	18.8	0.6	18.8		
12/29/41	Digoxin	0.5	142-150 (146)	3	19.2	28.0	30.8	35.6		34.2	28.0		2.1	0.7			0		0					
1/ 3/42	Digoxin	0.5	140-157 (151)	8-11	20.6	21.8	20.6	32.4	39.8	45.7	45.7		15.9	0	35.0	0	0	0	0	0	0	0		
1/ 9/42	Lanatoside C	0.63	154-174 (159)	7-9	8.8	14.5	18.2	28.4	35.2	40.4	33.4		0	0	18.2	0	0	0	0					
1/14/42	Oubain	0.375	155-174 (167)	2-4	22.2	34.2	41.3	44.3	50.4	46.8	16.8		22.2	4.2	18.6	0	0	0						
1/19/42	Digitoxin	0.5	162-176 (170)	45-48	2.9	7.1	5.9	5.9	6.5	29.4	10.6		35.3	11.2	25.3	1.7	3.5	5.9	0	0				
1/27/42	Oubain	0.375	174-180 (176)	1-3	26.8	22.9	29.0	23.8	29.6	49.5	31.2		27.3	26.2										
1/30/42	Digitoxin	0.5	122-132 (125)	30-34	0	0	0	13.6	30.4	24.8	17.7		22.4	18.4	14.4	0.8	0							

*The number in parenthesis indicates the most representative rate.

not apparent until the next day. Between these two were digoxin and lanatoside C; digoxin was slightly more rapid in its action. The ventricular rate began to slow within three to eight minutes after digoxin (Figs. 2 and 3), and within seven to nine minutes after lanatoside C (Fig. 4). The final quantitative effect produced by a given glycoside varied somewhat with the degree of decompensation, but the pattern of the response to each glycoside remained the same (compare digoxin Fig. 2 with Fig. 3, ouabain Fig. 5 with Fig. 7, and digitaline Nativelle Fig. 6 with Fig. 8; Table I).

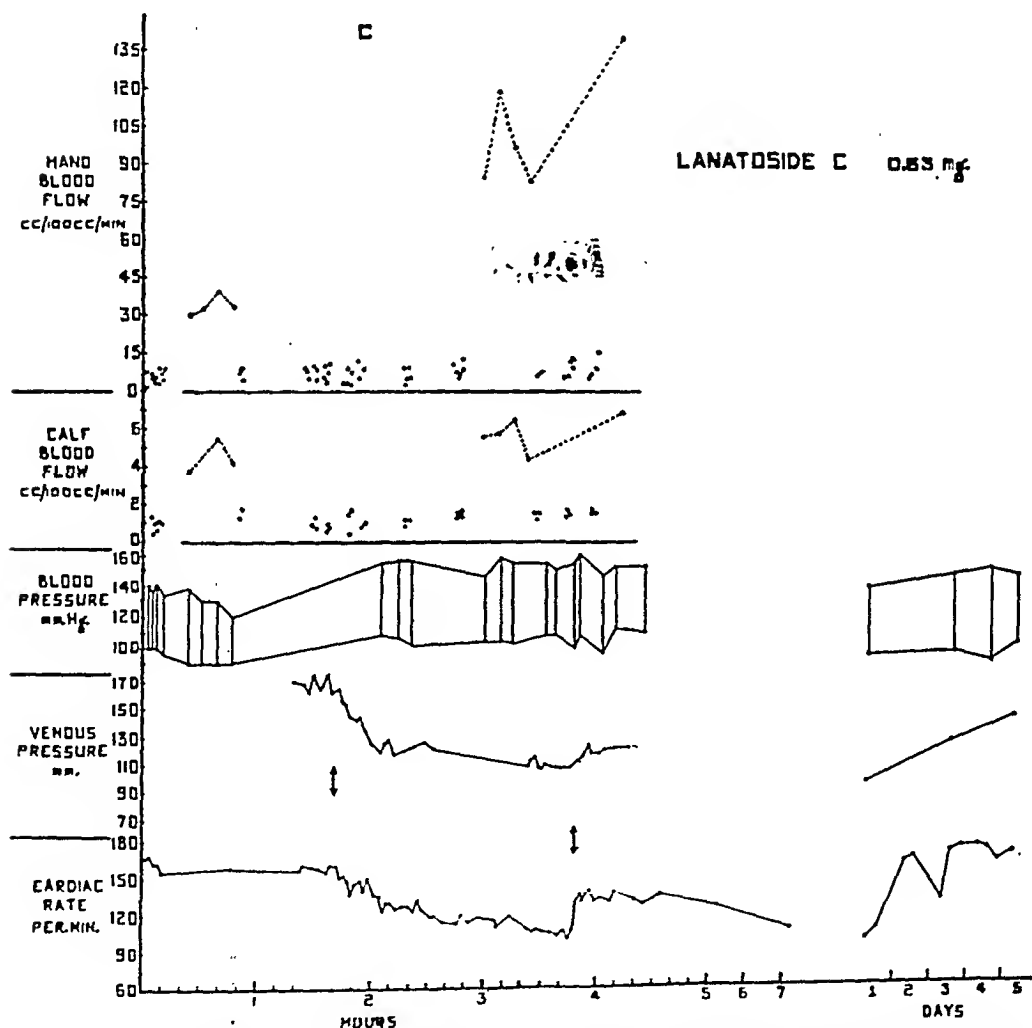


Fig. 4.—Circulatory effects following 0.63 mg. lanatoside C administered intravenously. Degree of decompensation quite severe. In this and subsequent charts the letter C indicates the point at which the Cheyne-Stokes respiration disappeared following administration of the glycoside.

Venous Pressure.—The venous pressure fell rapidly to normal after the administration of each glycoside (Table II). Again, ouabain initiated effects most rapidly, within three minutes (Figs. 5 and 7), and digitaline Nativelle most slowly, after twenty-five to thirty minutes (Figs. 6 and 8). After both digoxin (Figs. 2 and 3) and lanatoside C

(Fig. 4), the initiation of effect, four to eight minutes, was but slightly less rapid than after ouabain.

The decrease in venous pressure did not necessarily parallel the slowing in ventricular rate. For example, the first administration of digitaline Nativelle (Fig. 6) induced a considerable fall in the venous pressure but very little change in the ventricular rate. After lanatoside C (Fig. 4), the venous pressure decreased more rapidly than the cardiac rate. Ouabain on each of two trials lowered the venous pressure to 88 mm. of saline (Figs. 5 and 7). The concomitant changes in cardiac rate differed considerably. On the first occasion the ventricular rate fell to 90 per minute (Fig. 5), and, on the second, to 120 per minute (Fig. 7).

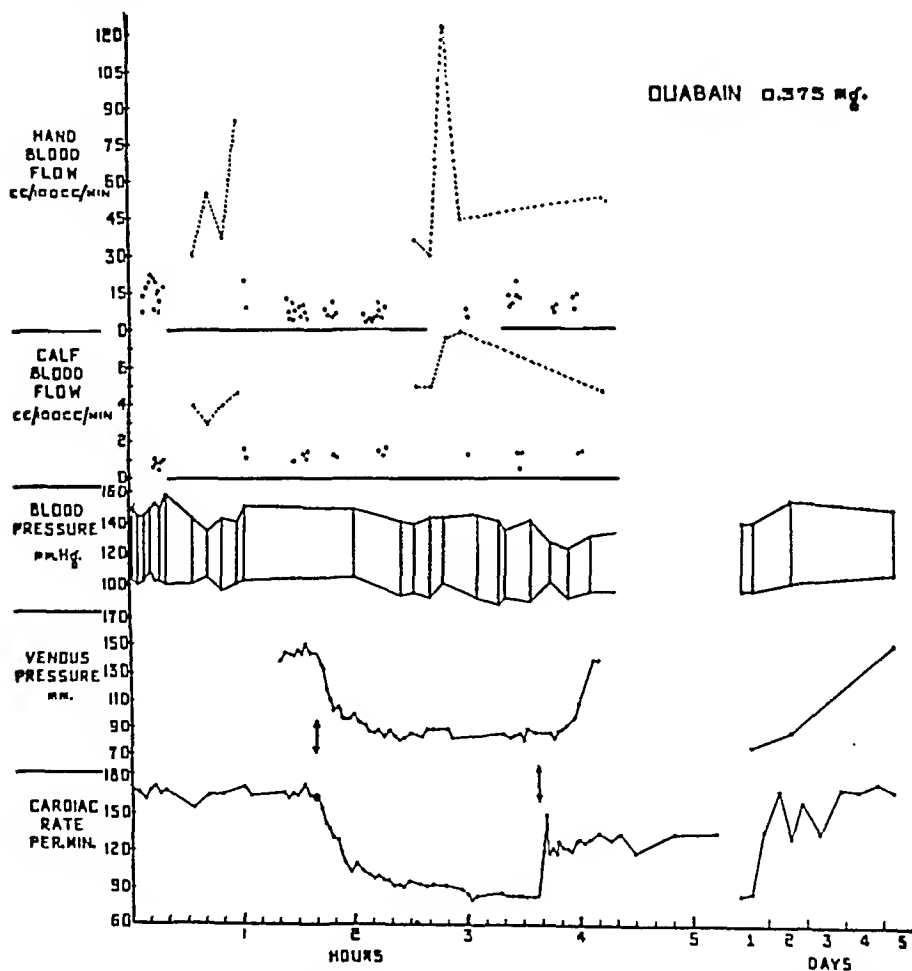


Fig. 5.—Circulatory effects induced by 0.375 mg. ouabain administered intravenously. Degree of decompensation moderate. Atropine sulfate caused much tenseness, restlessness, and involuntary muscular movements. To this was attributed the rise in venous pressure after atropine.

Finally, when vagal tone was released by the injection of atropine sulfate at a time when therapeutic effects had become established, the ventricular rate increased sharply, but the venous pressure remained unchanged (Figs. 2 and 4).

Arterial Blood Pressure.—After the injection of the glycosides the systolic pressure usually rose, whereas the diastolic pressure remained relatively constant. As a result, the pulse pressure increased. These changes were most marked when the circulation was very poor and the pulse pressure small, for example, after the second injections of ouabain (Fig. 7) and digitaline Nativelle (Fig. 8). When the circulation was somewhat better and the pulse pressure was already normal, the arterial pressure remained relatively constant, even though the venous pressure and ventricular rate decreased markedly; for example, the first injection of digoxin (Fig. 2).

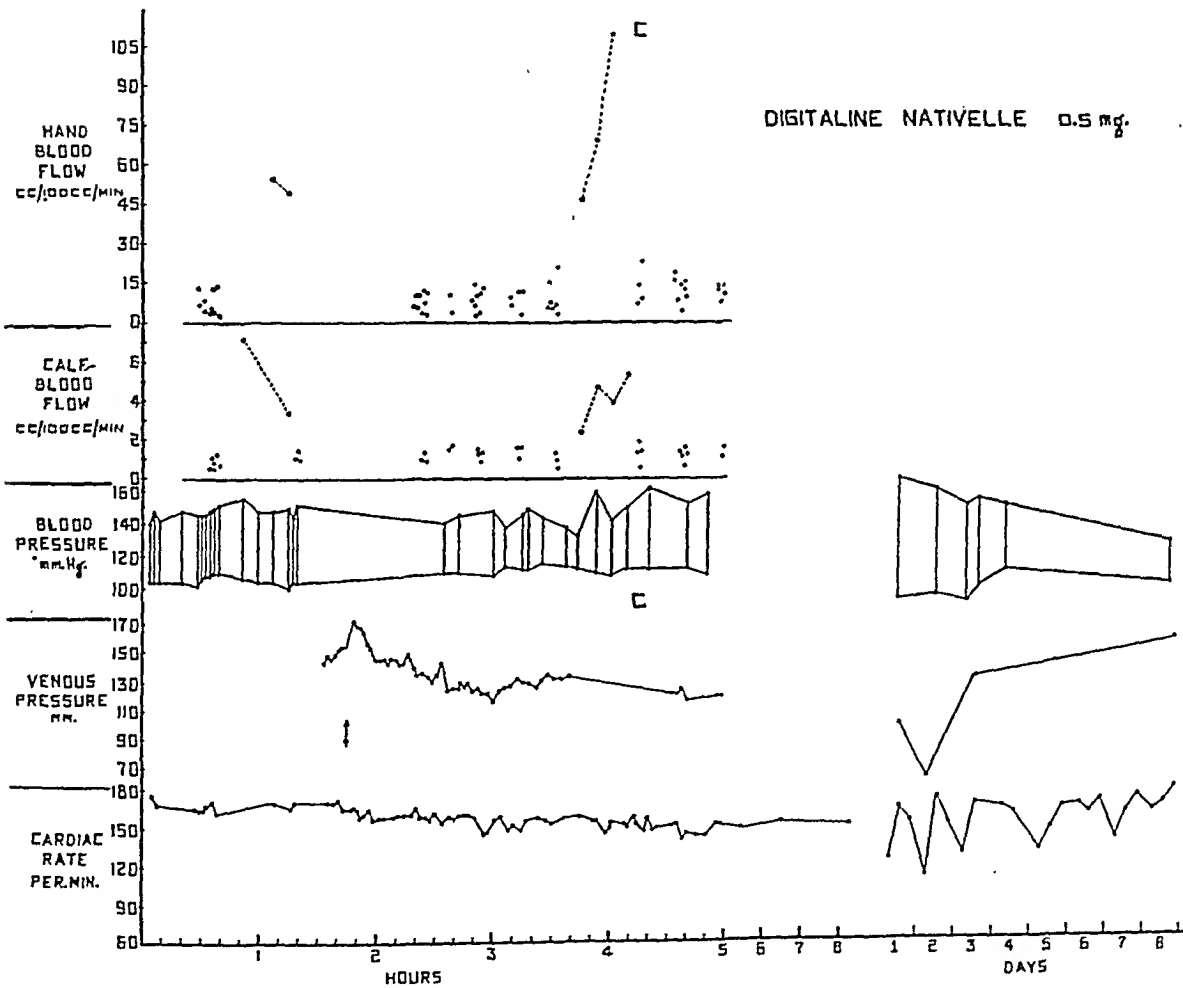


Fig. 6.—Circulatory effects induced by 0.5 mg. digitaline Nativelle given intravenously. Degree of decompensation quite severe.

Peripheral Blood Flow.—The return of the venous pressure and ventricular rate to normal was not accompanied by a significant alteration in the volume of blood flow to the resting hand and calf (Figs. 3, 4, 5, and 6). During reactive hyperemia the blood flow changed equivocally, or not at all, and often the changes in the blood flow to the hand were not even in the same direction as those to the calf (Figs. 3, 4, 5, and 6).

Respiration.—On three occasions Cheyne-Stokes respiration was present when a glycoside was given (lanatoside C, ouabain, digitaline Nativelle). Normal respiration was restored fourteen minutes after lanatoside C (Fig. 4), and twenty-eight minutes after ouabain (Fig. 7), but more slowly, fifty-two minutes, after digitaline Nativelle (Fig. 6).

Electrocardiograms.—The initial therapeutic effects induced by the four glycosides were not accompanied by significant changes in the electrocardiogram, other than a slowing of the ventricular rate.

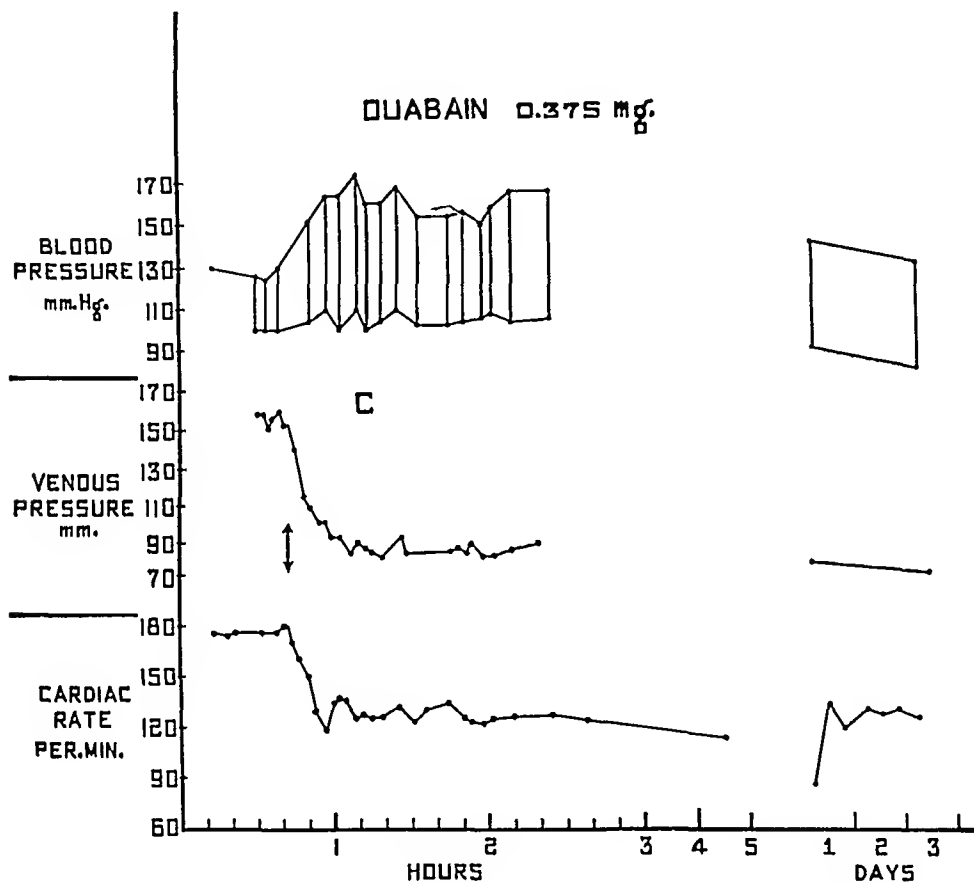


Fig. 7.—Circulatory effects induced by 0.375 mg. of ouabain given intravenously. Patient had incipient pulmonary edema and the degree of decompensation the most severe throughout the study.

Teleoroentgenograms.—The size and shape of the cardiac silhouette showed no, or little, change when teleoroentgenograms made during the initial therapeutic effects were compared with those taken before administration of the glycosides.

Release of Vagal Tone.—After the injection of 2.0 mg. of atropine sulfate, the ventricular rate increased sharply. It usually reached a maximum which was midway between the high initial value before the injection of the glycosides and the lowest value before the atropine was

administered (Figs. 2, 3, 4, and 5). This increase in ventricular rate was not accompanied by a significant change in venous pressure, arterial blood pressure, or volume of blood flow to the calf and hand.

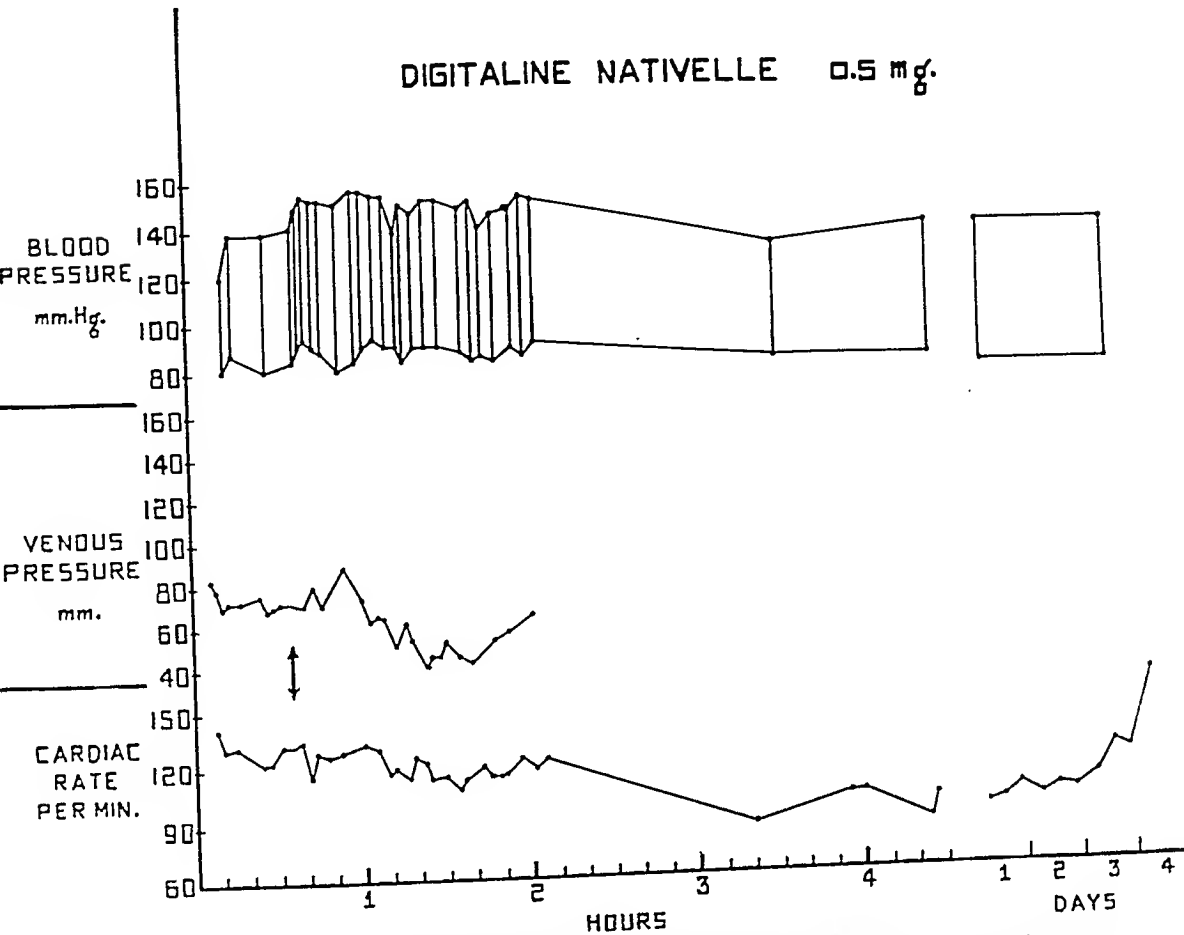


Fig. 8.—Circulatory effects induced by 0.5 mg. digitaline Nativelle given intravenously. Decomensation was less than at any other time, but patient was stuporous because of cerebral infarction.

DISCUSSION

This study is reported because the four glycosides were compared under conditions which were more adequately controlled than is usually possible. From observations on one patient a final concept cannot be formulated concerning the mode of action of these glycosides or the differences between them. However, it is significant that studies on other patients who recovered from heart failure after taking a single glycoside confirm many of the data here presented.

The administration of equal gram-molecular doses permits a comparison of the glycosides in terms of molecule for molecule. This is not necessarily equivalent to a comparison in terms of effective or therapeutic doses. It was not the purpose of this study to ascertain whether varying the dose of a glycoside would change the rapidity with which it produced effects. Certainly, compared molecule for molecule, onabain achieved therapeutic effects most rapidly, and digitaline Nativelle most slowly.

Between these two, but resembling ouabain more closely, were digoxin and lanatoside C; the former was slightly more rapid in its action. These differences in the actions of the glycosides are not yet explicable on the basis of their chemical structure or physical chemical properties.

When administered intravenously, the cardiac glycosides induced changes in several of the components of the circulation with surprising rapidity. Most noteworthy was the rapid reduction of the elevated venous pressure to normal (usually within thirty minutes to two hours). This change did not necessarily parallel the change in ventricular rate. It occurred without significant alteration in the volume of the peripheral blood flow and without change in the size and shape of the cardiac silhouette. Concomitantly, Cheyne-Stokes respiration disappeared.

In the absence of data on cardiac output, this study does not explain the mode of action of the cardiac glycosides. It does, however, indicate a method which, when amplified by the addition of serial measurements of cardiac output, gives promise of clarifying the controversy⁸⁻¹¹ concerning the mode of action of digitalis and its component glycosides.

SUMMARY

1. In a case of auricular fibrillation and congestive heart failure the circulation compensated promptly, but temporarily, after each intravenous administration of lanatoside C, digoxin, digitaline Nativelle, and ouabain. The drugs were given successively and in equal gram-molecular amounts.

2. When compared molecule for molecule, ouabain initiated effects most rapidly, and digitaline Nativelle most slowly. Between the two, but resembling ouabain more closely, were digoxin and lanatoside C; the former was slightly more rapid in its action.

3. When the cardiac glycosides were administered intravenously they produced abrupt changes in several circulatory functions without alterations in others:

- a. Elevated venous pressure fell quickly to normal.
- b. Rapid ventricular rate slowed promptly.
- c. Diminished arterial pulse pressure increased as a result of elevation of the systolic pressure.
- d. Volume of the blood flow to the calf and hand remained unaltered.
- e. Cheyne-Stokes respiration speedily disappeared.
- f. Cardiac size and shape did not change.
- g. Electrocardiograms showed only a slowing of the ventricular rate.

The authors wish to thank Dr. Arthur C. DeGraff for his advice and helpful criticism throughout this study. This investigation was conducted with the technical assistance of Miss Bertha Rader and Miss Helen Pomykala.

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SUBARACHNOID HEMORRHAGE CAUSED BY RUPTURED INTRACRANIAL ANEURYSM

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THE term "spontaneous subarachnoid hemorrhage," which has been used for many years to designate meningeal bleeding of nontraumatic origin, is confusing and meaningless, and should be discarded. This viewpoint was emphasized by Smith,¹ Ayer,² and Sands.³ In the majority of instances, such conditions as ruptured intracranial aneurysm, extension of a massive cerebral hemorrhage into the subarachnoid space, hemorrhage from a neoplasm, meningeal inflammation, or a blood dyscrasia can be established as the cause.

Our attention has been directed to the importance of recognizing aneurysm of the circle of Willis and its adjacent branches as the cause of the bleeding. We feel that aneurysms are responsible for the majority of examples of subarachnoid hemorrhage of nontraumatic origin.

In this report we wish to review the clinical features in 64 cases in which a diagnosis of subarachnoid hemorrhage caused by ruptured intracranial aneurysm was made. We also wish to discuss the pathologic observations on twelve patients who died as the result of rupture of aneurysms located in and around the circle of Willis. In none of these cases was there evidence of bacterial endocarditis or other types of septicemia. We are aware of the possibility that unrecognized trauma, hemorrhage from a neoplasm, or subarachnoid bleeding secondary to massive cerebral hemorrhage might have occurred in the cases in which the patients survived. The clinical features, however, are sufficiently definite to enable one to make the correct diagnosis in the majority of instances. This group of patients was examined at the University Hospital in the ten-year period from 1932 to 1942.

The literature is replete with discussions of aneurysms of cerebral vessels. McDonald and Korb,⁴ for example, reported 1,125 cases of saccular aneurysms of arteries at the base of the brain in which the diagnosis was verified by autopsy or operation. Another comprehensive review of the subject was made by Richardson and Hyland,⁵ who studied 118 patients with subarachnoid hemorrhage and eight patients with large, unruptured aneurysms over an eleven-year period.

The etiologic factors can be grouped under the following headings: congenital weakness of vessel walls, arteriosclerosis, inflammation, and trauma. The importance of congenital weakness of the vessel walls in

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the production of aneurysms was pointed out by Eppinger,⁶ and has been emphasized by Fearnside,⁷ Turnbull,⁸ Forbus,⁹ and Courville and Olsen.¹⁰ The fact that such hemorrhages have occurred in young persons has led numerous observers to conclude that a congenital defect must be the underlying cause. Anomalies in the vessels of the circle of Willis are thought by some authors to be contributory.^{11, 12} On the

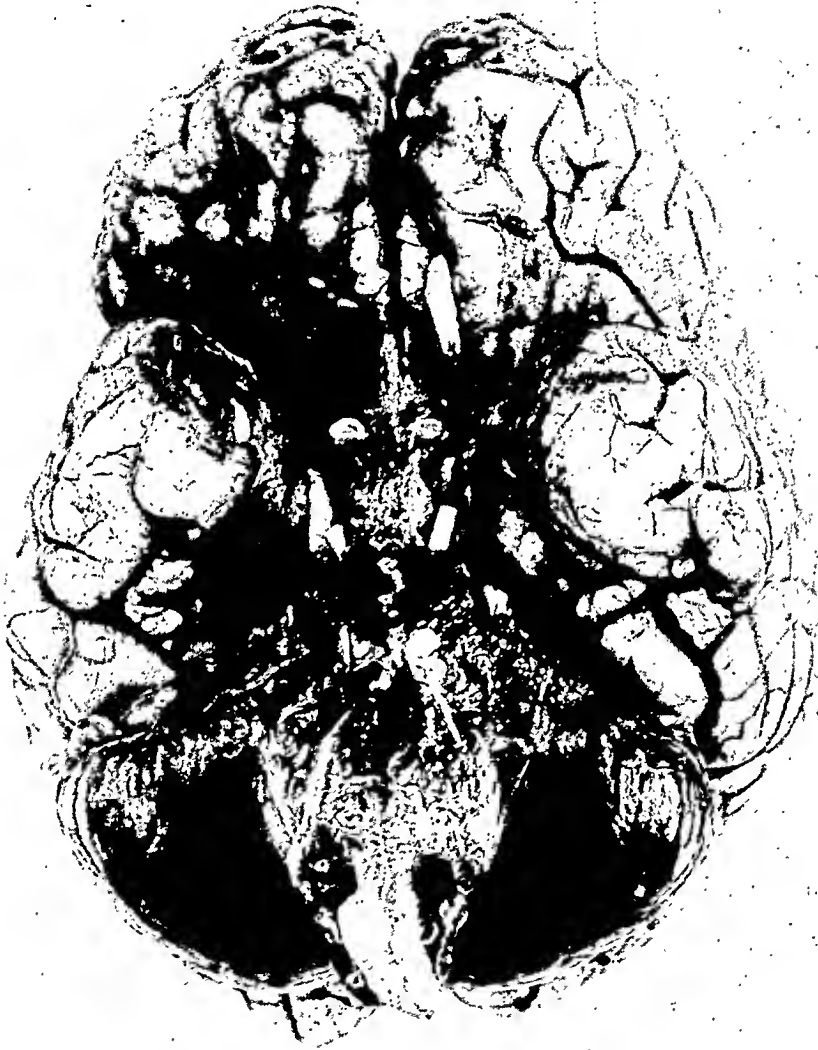


Fig. 1.—Massive subarachnoid hemorrhage resulting from rupture of aneurysm of left internal carotid artery.

other hand, Ellis¹³ regarded arteriosclerosis as the cause of these aneurysms. His view was shared by Tuthill,¹⁴ Symonds,¹⁵ and Strauss, Globus, and Ginsburg.¹⁶ "Mycotic" aneurysms have been reported by Ponfick,¹⁷ and Esser.¹⁸ In the opinion of Cushing,¹⁹ many aneurysms of early life are of mycotic, rather than congenital, origin. Syphilis and trauma play a minor role.

The most common finding at autopsy is a mass of clotted blood filling the subarachnoid space at the base of the brain (Fig. 1). Variable amounts of blood are extravasated over the convexity. The hemorrhage may occur into the ventricular system, as well. Occasionally, the blood will dissect through a lobe of the brain, and, rarely, may break into the subdural space (Fig. 2). Sometimes the aneurysm can be found without difficulty in the mass of clotted blood. We would like, however, to emphasize the importance of fixing the entire brain in formalin if the source of bleeding cannot be ascertained at once. In many instances the aneurysm will be found only when careful dissection of the circle of Willis and its adjacent branches is carried out after the brain is properly fixed (Fig. 3).

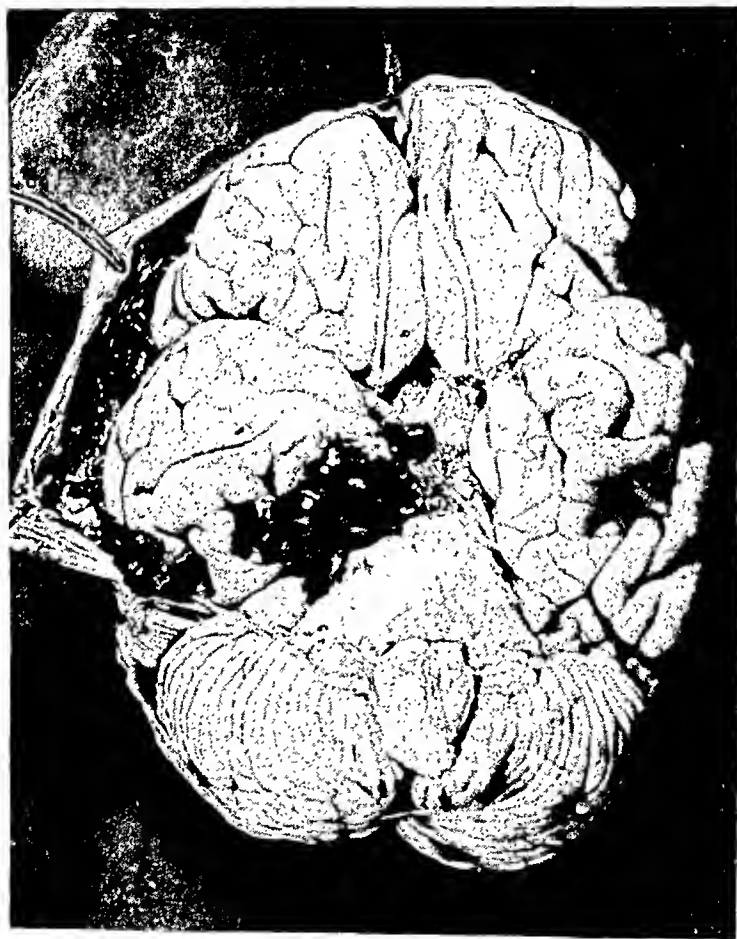


Fig. 2.—Ruptured aneurysm of right internal carotid artery, with extravasation of blood through right temporal lobe and leptomeninges, producing a subdural hematoma over right frontal, parietal, and temporal lobes.

We have examined the aneurysms microscopically in twelve autopsy cases (Table I). Six of the aneurysms were removed in toto, embedded in celloidin, and sectioned serially. The occurrence of these aneurysms at points of bifurcation is a well-established fact (Figs. 3, 4, and 8).

Microscopically, the aneurysmal wall is thin. The vessel, composed principally of fibrous tissue, undergoes progressive stretching and thinning until it ruptures (Fig. 5). In most instances the aneurysmal sac takes various stains poorly; hyalinization is common. The intimal lining is usually intact up to the point of rupture. In some of the specimens,

TABLE I

PRINCIPAL AUTOPSY OBSERVATIONS IN TWELVE CASES OF INTRACRANIAL ANEURYSM

AGE (YR.)	SEX	LOCATION	DIRECTION OF RUPTURE	PROBABLE CAUSE	COMMENTS
33	M	L. int. Carotid	Subarachnoid space	Congenital	Death after craniotomy Leptomeninges extensively thickened
51	F	L. int. Carotid	Subarachnoid space Intraventricu- lar via floor of third ventricle	Congenital	Small right internal carotid and left vertebral arteries
32	M	L. post. Cerebral	Subarachnoid space	Congenital	Positive Wassermann Extensive vascular syphilis in arteries other than an- eurysm
51	M	R. ant. Cerebral	Subarachnoid space Intracerebral (frontal)	Inflammatory (?)	Cultures and special stains for bacteria were negative
24	M	L. int. Carotid	Subarachnoid Intracerebral (frontal) Intraventricu- lar	Congenital	Polycystic kidney disease
59	M	R. middle Cerebral	Subarachnoid Intracerebral (temporal) Intraventricu- lar	Congenital	Extensive arteriosclerosis elsewhere; encephalomala- cia, right parietal lobe
45	M	R. middle Cerebral	Subarachnoid Intracerebral (temporal)	Arteriosele- rotic	Encephalomalacia, right temporal
37	M	Basilar	Subarachnoid Intraventricu- lar via floor of third ventricle	Congenital	
38	F	R. int. Carotid	Subarachnoid Intracerebral (temporal) Subdural	Congenital	Massive, recent, subdural hemorrhage
53	M	Ant. Communi- cating	Subarachnoid Intracerebral (frontal) Intraventricu- lar	Inflammatory	Acute arteritis at point of rupture
44	M	Ant. Communi- cating	Subarachnoid Intracerebral (frontal) Intraventricu- lar	Congenital	Anomalous anterior cerebral arteries
45	F	R. middle Cerebral	Subarachnoid Intracerebral (temporal)	Congenital	Polycystic kidney disease

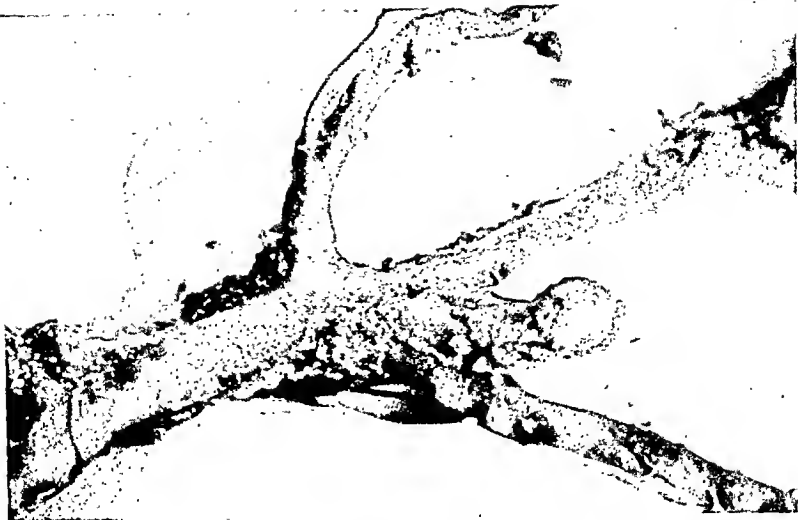


Fig. 3.—Small aneurysm located at the first bifurcation of the right middle cerebral artery. Although the point of rupture was not demonstrated grossly, it was readily identified in serial sections after embedding the specimen in toto in celloidin.



Fig. 4.—Dissection of entire circle of Willis to show ruptured aneurysm of basilar artery (A) at the point at which it bifurcates to form the two posterior cerebral arteries.

irregular thickening of the subintimal zone is seen (Fig. 5). In nine of the twelve specimens it was possible to demonstrate, with Weigert's elastic tissue stain, the presence of an internal elastic membrane which was very attenuated and defective, particularly at the points of rupture (Fig. 6). Occasionally one finds bits of media, but the amount of muscle tissue is so small as to be almost valueless from the functional standpoint. In most instances, no inflammatory reaction is present. In two of the specimens, however, some infiltration of the aneurysm wall by inflammatory cells, principally lymphocytes, was seen (Fig. 7). In one of these (Fig. 7), a zone of inflammatory elements extended through the wall at a place removed from the point of rupture. The basic aneurysmal process, especially fragmentation of the media, remains the same. In the other specimen the appearance was more nearly that of a true mycotic aneurysm. By way of summary, then, the following changes are seen in greater or lesser degree: thinning of the aneurysmal wall, hyalinization and fibrosis of the wall, proliferation of the intima, attenuation and straightening of the elastic membrane, thinning or absence of the media, and cellular infiltration.



Fig. 5.—Aneurysm located at first bifurcation of right middle cerebral artery. Although there was extensive arteriosclerosis elsewhere, aneurysmal wall is thin. There is extensive fragmentation of vessel wall, especially at the point of rupture. One small area of intimal thickening is seen. Hematoxylin-eosin stain. $\times 75$.

From our observations, we would subscribe to the theory of congenital weakness of the vessel wall as the factor responsible for the majority of these aneurysms. Our studies indicate that, for the most part, we are dealing with a long-standing disorder which results in progressive



Fig. 6.—Aneurysm of the first bifurcation of the right middle cerebral artery. The point of rupture is at (R). Note the fragmentation of the elastic layer and the patchy thickening of the intimal layer. Weigert's elastic tissue stain, $\times 15$.



Fig. 7.—Aneurysm of right middle cerebral artery, showing zone of inflammatory cells in only one portion of the wall at some distance from point of rupture. The thinning of the wall, fibrosis, and defect in elastica are well seen. Hematoxylin-eosin stain, $\times 75$.

stretching of the vessel wall to the bursting point. The occurrence of these lesions at bifurcations, the presence of anomalies in the circle of Willis (Figs. 8 and 9) and other conditions, such as polycystic kidney disease, further strengthen the theory of the congenital nature of these aneurysms. Elevated blood pressure probably plays a part in the ultimate rupture of the vessel. It is difficult to evaluate the importance of other factors, such as ageing of the vessel and toxic or degenerative influences.

A common immediate sequel to rupture of a vessel of the circle of Willis or its larger branches is extravasation of blood into the subarachnoid space (Fig. 1, Table II). The irritating effect of blood produces signs and symptoms of meningitis. Another phenomenon which is often encountered is the local pressure effect of the enlarging aneurysm or of the effused blood. The optic nerves and tracts and the oculomotor nerves are often involved. Blood may be forced through the brain substance, with the production of other focal signs. Intraventricular rupture has been frequent in the cases in which the patients died (Table I).

The condition under consideration is a disease of middle age. The average age of our patients was 43 years. The oldest patient in our series was 72 years of age, and the youngest, 14 years. The sex distribution was approximately equal. In only ten of our cases did some form of severe mental or physical strain precede the rupture; the majority of ruptures occurred during ordinary activity.

The onset is usually abrupt. Characteristically, there is sudden, severe pain in the head or in the back of the neck. The headache is usually of a diffuse type, but in some cases the pain takes a definite localizing character in one temple or behind the eye. Nausea and vomiting occur with considerable frequency. Visual disturbances of one type or another are commonly experienced. Convulsions occur occasionally. When convulsions are present they are usually generalized in type. Consciousness may or may not be lost after rupture of an aneurysm.

The clinical signs are usually quite characteristic. When blood is extravasated into the subarachnoid space, it gives rise to the symptoms of meningitis, namely, stiffness of the neck and a positive Kernig's sign. There is usually a mild febrile reaction which lasts while the blood is being absorbed. A rise of temperature to 103 or 104° F. in the absence of pneumonia and in the presence of increasing coma usually indicates intraventricular bleeding. Hemiparesis or hemiplegia is caused by pressure of the extravasated blood upon the cerebral peduncles, laceration of brain substance by effused blood, or softening of the brain in the area supplied by the involved vessel.

CASE REPORTS

CASE 1 (R. W.).—Rupture of intracranial aneurysm, with subarachnoid hemorrhage, following exertion. Similar attack one month later. Bloody spinal fluid. No localizing signs. No recurrence of symptoms in subsequent seven months.



Fig. 8.—Aneurysm of the anterior communicating artery, showing point of rupture. The left anterior cerebral artery (A) is rudimentary, and does not communicate with the aneurysm, but joins the large left branch (A') arising from the region of the aneurysm. The major portion of the vascular supply is thus carried through the right anterior cerebral artery (B), from which vessel the aneurysm and two normal-sized anterior cerebral arteries (A') (B') emerge.

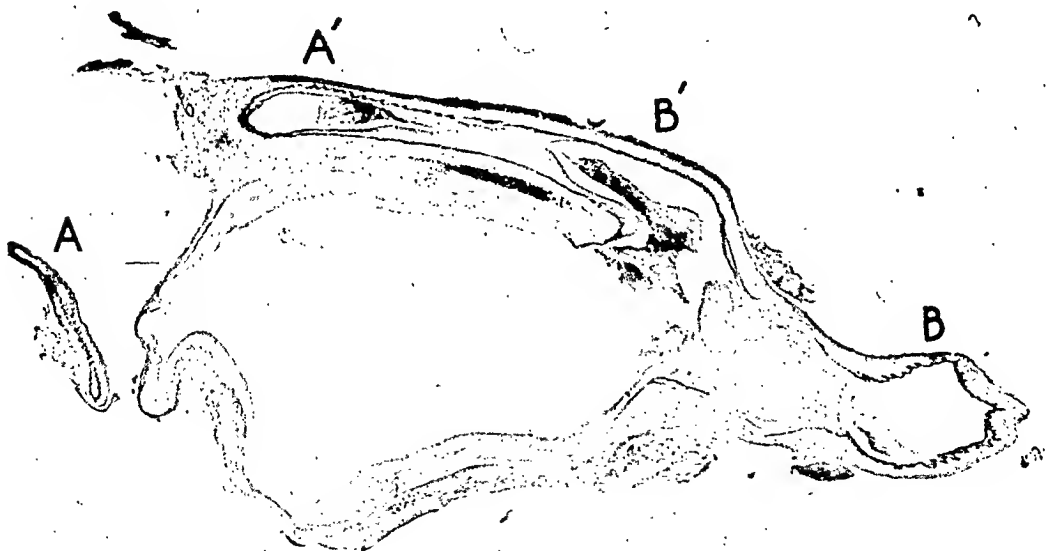


Fig. 9.—Section of aneurysm shown in Fig. 8. Identification markings as above. Weigert's elastic tissue stain, $\times 6$.

TABLE II
SUMMARY OF CLINICAL STUDIES OF 64 PATIENTS WITH SUBARACHNOID HEMORRHAGE

AGE INCIDENCE	SEX INCIDENCE	FACTORS PRECED- ING RUPTURE	INITIAL SYMPTOMS	SIGNS*	CLINICAL RESULT AT DISCHARGE
By decades:	Male 33	Marked ex- 10	Headache	Stiff neck	Died 18
First	Female 31	ertion	Vomiting	Positive Kernig's sign	Well 22
Second		Mild ex- 32	Dizziness	Fever	With sequelae 24
Third		ertion	Unconsciousness	Hemiparesis or hemi- plegia	Hemiparesis or hemi- plegia 6
Fourth		None 22	Visual disturbances	Ocular palsy	Ocular palsy 11
Fifth			Mental confusion	Choked discs	Visual field disturbances 3
Sixth			Convulsions	Aphasia	Aphasia 2
Seventh				Visual field defect	Other 2
Eighth				Nystagmus	
Oldest, 72 years				Bruit	
Youngest, 14 years				Hypertension (arterial)	
Average, 43 years				Marked	
				Moderate	
				Spinal Fluid Examination	
				Pressure:	
				Over 200 mm.	17
				Below 200 mm.	47
				Color:	
				Grossly bloody	32
				Xanthochromic	16
				Clear	13

*Approximately 25 per cent of these patients were admitted to the hospital several weeks after the beginning of the bleeding.

This 14-year-old boy was well until October, 1941, when he developed a severe headache after a short period of exercise. Within fifteen minutes he began to vomit because of the headache. He remained in bed two weeks, during which time his headache gradually subsided. He was well until Nov. 13, 1941, when he suddenly developed headache, again after exertion. He vomited hourly during the night, complained of a stiff neck, and became irrational.

Examination on admission to the hospital on Nov. 14, 1941, showed that he was well developed and well nourished. His temperature was 98.6°, his pulse rate, 72, and his respiratory rate, 20. There was considerable photophobia. His neck was stiff, and Kernig's sign was present. His blood pressure was 110/80. The spinal fluid was under an initial pressure of 175 mm., and was grossly bloody. The blood and spinal fluid Wassermann reactions were negative. Five days later the spinal fluid was under an initial pressure of 105, was xanthochromic, and contained 1,250 erythrocytes per c. mm. Examination of the urine and blood showed nothing remarkable.

For a period of two days after admission he complained of severe headache and vomited frequently. These symptoms gradually subsided, and, by the time of discharge from the hospital, Nov. 22, 1941, he was free of symptoms except for a very mild headache. He had no further attacks up to the time of his last examination, June 6, 1942, at which time he felt well and exhibited no abnormal neurologic signs.

CASE 2 (W. J.).—Three separate subarachnoid hemorrhages. Residual paresis of cranial nerves.

This 56-year-old foundry worker was first admitted to the University Hospital April 4, 1936. His past history was unimportant except for the fact that he had had a fall in 1935, involving the right temporal region, and suffered from a headache for a period of one day. On Feb. 13, 1936, he developed a sudden, severe pain in the right temporal and occipital regions, with vomiting and stupor. Spinal punctures revealed increased pressure and bloody spinal fluid. The second attack occurred Feb. 24, 1936, when, in addition to the severe headache, he developed ptosis of the right upper lid and experienced double vision when the lid was held up.

Examination on admission, April 4, 1936, showed percussion tenderness over the right temporoparietal region, complete oculomotor nerve paralysis on the right side, and evidence of generalized arteriosclerosis. His blood pressure was 130/85, and his blood Wassermann reaction was negative. The spinal fluid examination was negative. He improved slightly with rest in bed and sedatives. At time of discharge his oculomotor paralysis had diminished.

He worked daily until August, 1941, when he was suddenly seized with severe occipital and cervical pain. A spinal puncture revealed bloody fluid. He improved slightly until the time of his second admission to the hospital, Aug. 15, 1941. Additional abnormalities at this time were right abducens paresis and a positive Babinski sign on the left. The spinal fluid was subsequently xanthochromic, was under an initial pressure of 250 mm., and contained 105 mg. of protein per 100 c.c. All of the new signs disappeared, so that, by August 21, he exhibited only the right-sided oculomotor paresis.

He returned to work, but relapsed on Nov. 10, 1941, and again on Dec. 27, 1941. After this last attack he was again admitted to the hospital,

where he remained for several weeks. He refused to have a diagnostic arteriographic examination or exploratory craniotomy performed.

CASE 3 (J. M.).—Two subarachnoid hemorrhages six years previous to the fatal attack. Sudden onset of severe headache after exertion, unconsciousness, slight improvement, then relapse and death in five days. Grossly bloody spinal fluid. Autopsy: congenital aneurysm of anterior communicating artery, with anomalous anterior cerebral artery.

The patient was 44 years old. In December, 1936, this patient suddenly experienced severe headache, vomiting, stiffness of the neck, and bradycardia. There was no loss of consciousness at any time during this attack. Neurologic examination showed no focal cerebral signs. Lumbar puncture eight days later revealed xanthochromic fluid. After the removal of 15 c.c. of spinal fluid he obtained relief from the headache and felt well until January, 1937, when another hemorrhage occurred. In this attack he was unconscious for several weeks. A total of nine spinal drainages were performed. Again, there were no definite signs indicating the exact site of the ruptured vessel. He recovered from this illness much more slowly than from the previous one, but was able to resume his duties as a university professor in the fall of 1937. Neurologic examination at intervals showed nothing abnormal. His blood pressure ranged from 134/84 to 148/96.

On Feb. 26, 1942, he suddenly developed a severe headache following a short period of exertion, and soon became unconscious. One hour later he was admitted to the University Hospital in a stuporous condition. His temperature was 99.8° F. There were several flame-shaped hemorrhages in the right retina. His blood pressure was 220/146. He moved his arms and legs well, but there was a bilateral plantar extensor response. He was incontinent. The spinal fluid, which was grossly bloody, was under an initial pressure of 400 mm. The blood and spinal fluid Wassermann reactions were negative. He improved slightly during the following day, then gradually grew worse. Several more spinal punctures showed a grossly bloody fluid which was under increased pressure. He died on the fifth day. Terminally, his temperature rose to 107° F.

Autopsy was limited to the brain, which weighed 1,700 grams. Extensive hemorrhage was present throughout the entire subarachnoid space, especially around the base. After the brain was fixed in formalin, the vessels of the circle of Willis were dissected out. The right vertebral artery was one-half the size of the left. The anterior cerebral supply was anomalous (Fig. 8). The proximal portion of the left anterior cerebral artery was rudimentary. Most of the blood supply in this region was carried by way of the right branch. In the region of the anterior communicating artery there was a thin-walled aneurysm which measured 2 by 1.5 by 1.5 cm. The point of rupture was readily demonstrated. Two equal-sized anterior cerebral arteries arose from this aneurysm, and the filamentous anterior cerebral artery joined the left branch approximately 3 cm. distal to the aneurysm. There was considerable hemorrhagic softening of the medial surfaces of both frontal lobes. Bleeding had occurred into the ventricles by way of the anterior horns. The aneurysm was embedded in celloidin in toto and sectioned serially.

Microscopic sections were stained with hematoxylin and eosin, Masson's trichrome stain, and Weigert's elastic tissue stain. The aneurysm

(Fig. 9) was thin-walled and fibrotic. Bits of muscle tissue could be identified in the wall, in addition to a few fragmented remnants of the elastic layer. A few patches of intimal thickening were in evidence. There was no sign of inflammation in the wall of the aneurysm.

CASE 4 (D. B.).—Hypertension, headaches, and increasing irritability for five months. Unconsciousness, followed by restlessness and severe headache. Bloody spinal fluid. Second attack three weeks later, associated with convulsions. Death in twenty-five minutes. Autopsy: aneurysm of basilar artery, with rupture through floor of third ventricle and intraventricular hemorrhage.

The patient was 37 years old. This man was refused insurance seven years before admission because of hypertension. Five months before admission he began to complain of headaches which were worse in the morning, and his wife noticed that he was becoming increasingly irritable. However, he continued to work until nine days before admission, when, about 4 A.M. on Sept. 27, 1941, he began to breathe noisily and could not be roused. He recovered consciousness in two hours, then began to vomit. His physician found that his systolic blood pressure was 220 mm. Hg. He was given several hypodermic injections during the day. That evening he became very restless, and was taken to a local hospital, where he became disoriented, and, finally, stuporous.

When admitted to the University Hospital, Oct. 3, 1941, he was very drowsy. His head was retracted and his neck was stiff. Examination of the ocular fundi showed advanced hypertensive retinal disease. His blood pressure was 210/130. Examination of the urine showed a trace of albumin. The blood cell count was normal. The blood Wassermann reaction was negative. The spinal fluid was under an initial pressure of 50 mm., showed a positive Pandy test for globulin, 7 cells, a negative Wassermann reaction, and a positive test for blood.

He improved gradually at first. His drowsiness disappeared and he complained less of headache. During the night of Oct. 15, 1941, he developed a convulsion in his sleep, his respirations became stertorous, and he died within twenty-five minutes.

The brain weighed 1,740 grams. The basilar leptomeninges were filled with clotted blood. After the brain was fixed in formalin the circle of Willis was dissected free. Atheromatous changes were found in all the branches of the circle of Willis. At the bifurcation of the basilar artery there was an aneurysm the size of a cherry (Fig. 4). It had ruptured through the floor of the third ventricle and had filled the entire ventricular system with blood.

Serial sections were made of the basilar aneurysm after it had been embedded in celloidin. A control specimen was prepared from the right middle cerebral artery. These sections were stained with hematoxylin and eosin, Masson's trichrome stain, and Weigert's elastic tissue stain.

Sections of the basilar artery at its bifurcation showed a comparatively large rupture. Although the vessels elsewhere showed advanced atherosclerotic changes, the aneurysm was thin-walled, and consisted mostly of fibrous tissue which contained remnants of media and elastica. Only a few patches of intimal thickening could be seen. There was no evidence of inflammation in the aneurysm wall.

CASE 5 (E. R.).—Sudden onset of severe headache, followed by vomiting. Two days later, a second attack, followed by convulsion and stupor. Blindness, weakness of the right arm and leg. Papilledema, right-sided oculomotor paralysis. Bloody spinal fluid. Third attack ten days later, resulting in death. Autopsy: aneurysm of left internal carotid, with massive rupture through left temporal lobe into the left subdural space.

This 38-year-old housewife was admitted to the University Hospital Jan. 2, 1942, in a stuporous condition. Her husband gave the information that she had been in good health, except for mild epigastric distress, until the afternoon of January 2, when she suddenly called to him that something had broken in her head. She did not fall or lose consciousness, but immediately developed a headache and was forced to go to bed. Approximately five hours afterward she vomited. She remained in bed the following day because of moderately severe headache. On January 4, however, she awakened at 4 A.M., screaming because of pain in her head. She had a brief generalized convulsion and lapsed into stupor. Later in the morning, however, she could be roused. She complained that she was completely blind, and was mentally confused. Her right arm and leg were weak.

On admission to the hospital she was stuporous but responsive. Examination January 5 revealed ptosis of the right eyelid, a dilated and practically immobile right pupil, and external deviation of the right eye. There was bilateral papilledema, with vaginal sheath hemorrhages in both retinæ. Vision O.D., 6/30; O.S., light and shadow. Temperature, 102° F., pulse rate, 80, respiratory rate, 18. Her neck was very stiff to anteflexion. The blood pressure was 150/100. Examination of her extremities showed no evidence of weakness or changes in the reflexes or sensations. No bruit could be heard on auscultation of the skull.

Her urine was normal except for a trace of albumin. The erythrocyte count was 5.65 million, the hemoglobin, 14.0 grams, and the leucocyte count, 17,200. The blood smear was normal. The blood Wassermann reaction was negative. The initial pressure of the spinal fluid was 210 mm. with the patient in the horizontal position; the fluid was bloody, contained 40 leucocytes per c.mm., and gave a strongly positive reaction for blood and a negative Wassermann reaction.

She improved gradually, had less headache, and her vision returned. On the morning of January 12 her headache suddenly returned, she cried out, and had a generalized convulsion. Her respirations became shallow and rapid, and she died in forty minutes.

The important autopsy observations were confined to the brain, which weighed 1,450 grams. There were approximately 2½ ounces of freshly clotted blood in the right subdural space over the frontal, temporal, and parietal regions. The blood had come from the right internal carotid artery and had forced its way through the substance of the inferior portion of the right temporal lobe into the subdural space (Fig. 2). Blood had also extravasated into the temporal horn of the right lateral ventricle.

The aneurysm was thin-walled and fibrotic. The adventitia contained a few inflammatory cells, mostly lymphocytes. In other respects, however, the microscopic appearance was the same as that in the previous cases.

DIAGNOSIS

Ordinarily, the diagnosis of this condition is not difficult. The sudden onset of headache, symptoms and signs of meningeal irritation, and the presence of blood in the spinal fluid usually constitute sufficient evidence on which to make a diagnosis. Subarachnoid hemorrhage after trauma or during the course of one of the hemorrhagic disorders should present no unusual diagnostic difficulties. The sudden appearance of cranial nerve paralysis or visual field defect, with headache, suggests an intracranial aneurysm. If the meningeal syndrome appears, and if the spinal fluid is found to be bloody, the diagnosis is almost certain. Multiple sclerosis, brain tumors, and infections, such as cerebrospinal syphilis, should also be considered in the differential diagnosis. If the patient is seen several weeks or months after the attack, diagnostic difficulties may be increased. An expanding intracranial aneurysm, without rupture, will often be diagnosed as a cerebral neoplasm. Perhaps the most difficult problem of all is the differentiation from primary intracerebral hemorrhage. The history of previous rupture is of value. In cases of primary intracerebral hemorrhage the paralysis usually appears at the onset. In cases of ruptured aneurysm and extension of the bleeding intracerebrally, paralysis of the extremities is sometimes delayed. When the patients are unconscious and have bloody spinal fluid and a stiff neck, the correct diagnosis may not be possible.

A bruit is rarely heard over these aneurysms. Roentgenograms of the skull usually show nothing abnormal. Arteriographic examination of the cerebral vessels offers some hope of ascertaining the exact location of some of these lesions, but will often be disappointing in the case of the smaller aneurysms.

PROGNOSIS

In general, the prognosis is not good. Admittedly, in most of the cases which we have seen the disease was most severe. It is possible that a small defect in a vessel wall may heal without further trouble. However, if the patient survives one attack he is likely to have others. The immediate prognosis will often be in doubt. Decerebrate rigidity, a rising temperature, and the persistence of gross blood in the spinal fluid are ominous signs. The mortality is higher in older persons and in those who have arterial hypertension.

TREATMENT

The treatment of meningeal hemorrhage caused by ruptured intracranial aneurysm is principally symptomatic. Absolute rest in bed and analgesics are ordinarily recommended. Unusual exertion should be interdicted, and the patient should be kept in bed several weeks or more, depending upon how quickly his symptoms abate. The use of glucose intravenously is of questionable value in relieving the headache or

modifying the other symptoms. The question whether repeated spinal punctures should be done invariably comes up for consideration. From the diagnostic standpoint, spinal puncture is indicated. Occasional examination of the cerebrospinal fluid may be necessary to ascertain whether there is persistent bleeding; we have no evidence that spinal puncture is definitely harmful, or that repeated spinal drainage is of therapeutic value. In recent years neurosurgical procedures have been successfully utilized in the treatment of some of these patients. It is often difficult to locate the source of the bleeding, even when arteriographic examination is utilized.

CONCLUSIONS

The term "spontaneous subarachnoid hemorrhage" implies lack of knowledge concerning the cause of nontraumatic subarachnoid bleeding. In most of these cases, rupture of an aneurysm of the circle of Willis or its immediately adjacent branches is the source of the hemorrhage.

This study is based on the observation of 64 patients. In this group, the presence of an aneurysm was verified by post-mortem examination in twelve instances. The etiologic factors commonly given are congenital weakness of vessel walls, arteriosclerosis, inflammation, and trauma. We feel that long-standing structural weakness of the vessel wall, plus the mechanical factors induced at bifurcations, offers the most logical explanation for the majority of these aneurysms.

This is fundamentally a disorder of middle adult life, although bleeding may occur at any age. The most consistent symptom is sudden onset of pain in the head. The symptoms and signs of meningeal irritation make their appearance soon afterward. The presence of blood in the spinal fluid is a valuable aid in diagnosis.

Case reports are included to show variations in the clinical manifestations. Of the 64 patients examined, 18 died in the hospital, 22 were discharged well, and 24 were improved, but were left with sequelae, such as hemiplegia, ocular palsy, aphasia, and visual field disturbances.

The prognosis must be guarded in every case. Recurrences often take place. The mortality is higher in older people and in patients who have arterial hypertension.

The treatment is principally symptomatic. Rest in bed and sedatives are necessary during the acute phase. Avoidance of undue excitement is indicated. Repeated lumbar punctures are of doubtful efficacy. Some of the patients with large, localizable aneurysms can be improved or cured by surgical means.

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ELECTROCARDIOGRAPHIC CONSIDERATIONS IN SMALL ANIMAL INVESTIGATIONS

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INTRODUCTION

THERE have been several investigations in which the electrocardiograph has been used to study cardiac changes in small animals subjected to abnormal dietary conditions. Agduhr and Stenström¹ attempted to relate the electrocardiographic pattern to pathologic changes which resulted from feeding cod-liver oil to mice. Weiss, Haynes, and Zoll² studied the cardiac rate, electrocardiographic complexes, and the response of rats to drugs in repeatedly induced states of vitamin B₁ deficiency.

In one of our investigations, the electrocardiographic method was contemplated for use in the study of cardiac changes in rats and mice infected with *Trichinella spiralis*. We found, however, that the usual electrocardiographic apparatus was not adequate because of the exceedingly rapid heart rates of mice and rats. This report is, therefore, preliminary to further investigation in which electrocardiographic principles may be applied in small animal experimentation, such as experimental trichinosis, Chagas's disease, sarcosporidiosis, bacterial myocarditis, and vitamin B₁ deficiency.

PRELIMINARY OBSERVATIONS

Electrocardiograms were taken on white mice with a commercial amplifier type of electrocardiograph.† Typical mouse electrocardiograms obtained with this apparatus are shown in Fig. 1. Measurements of the electrocardiograms showed that the time of rise of the R waves was less than the galvanometric speed. From an electrical standpoint it is well known that any galvanometer which possesses an inherent speed which is less than the electrical impulse that is being graphically recorded must introduce distortion. The electrocardiographic tests were repeated with Einthoven string galvanometer electrocardiographs, and the same form of distortion was noted (Fig. 2). Similar distortion was also noticeable in the records taken by the authors mentioned in the introduction to this article.

To prove the assumption that distortion is present and that it is a function of galvanometric speed, an electronic electrocardiograph was

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constructed, in which the galvanometric speed was adjustable, and a series of electrocardiograms was taken on each mouse at progressively increasing speeds. A few series of such tests immediately showed that the electrocardiographic pattern of each mouse underwent a gradual change as the galvanometric speed was progressively increased. Furthermore, the electrocardiographic configuration at high string speed was entirely different from that at usual electrocardiographic string speeds (Fig. 3). The electrocardiograms of Fig. 3 were taken on the same mice as those of Fig. 2.

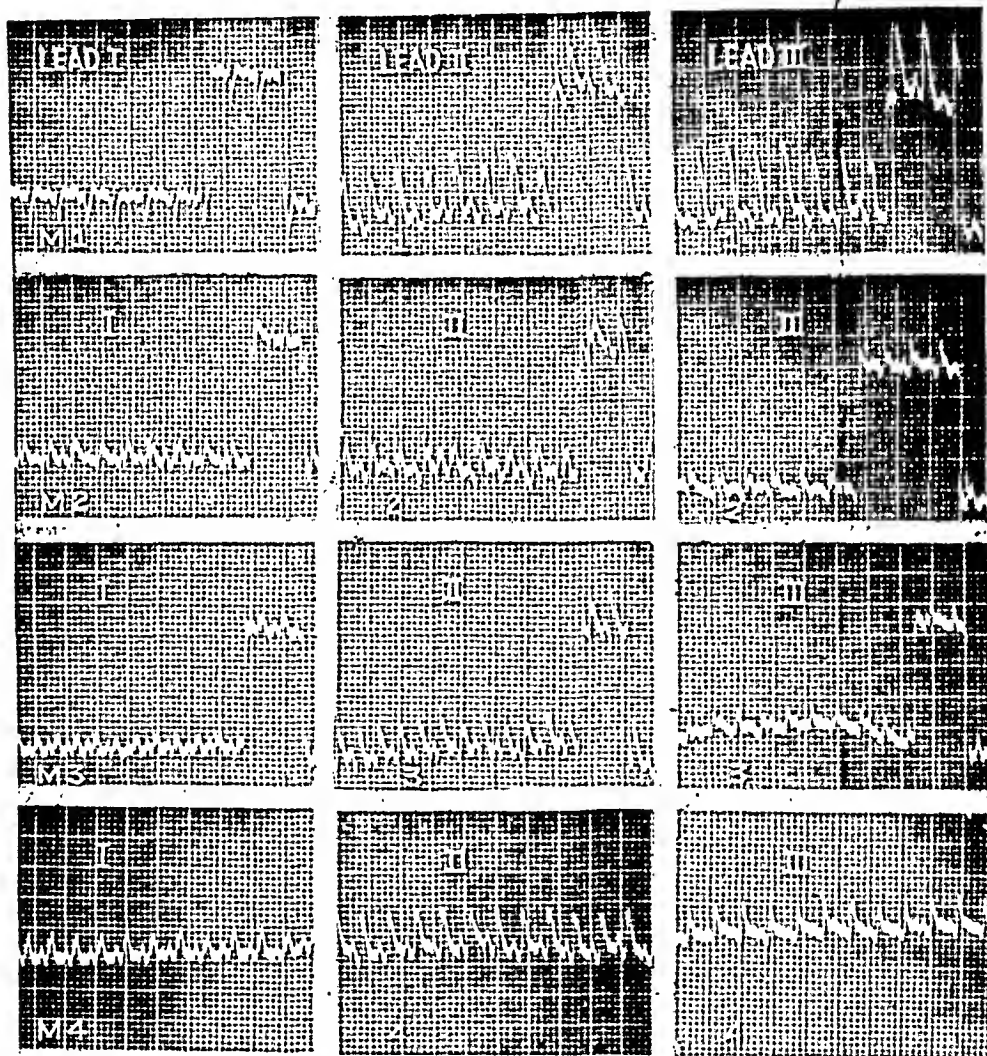


Fig. 1.—Typical appearance of four white mouse electrocardiograms obtained with a commercial amplifier-type electrocardiograph. The film speed is 50 mm. per second. The fine time lines are spaced 0.02 second and heavy time lines are spaced 0.10 second. The galvanometric speed is 0.01 second. The sensitivity is 2 cm. per millivolt.

ELECTROCARDIOGRAPHIC CONSIDERATIONS

The Theoretically Perfect Galvanometer.—When an electrocardiograph is standardized and the standardization is registered, a graph such as

that in Fig. 4, *A* should be recorded if the galvanometer is theoretically perfect. *AB* represents the isoelectric line. At point *B*, the millivolt standardizing potential is applied, and the galvanometer deflects one centimeter in zero time to point *C*. For the duration of the millivolt application, the galvanometer beam remains one centimeter above the isoelectric line. When the millivolt is removed at point *D*, the galvanometer beam drops to its original isoelectric level (*EF*) in zero time.

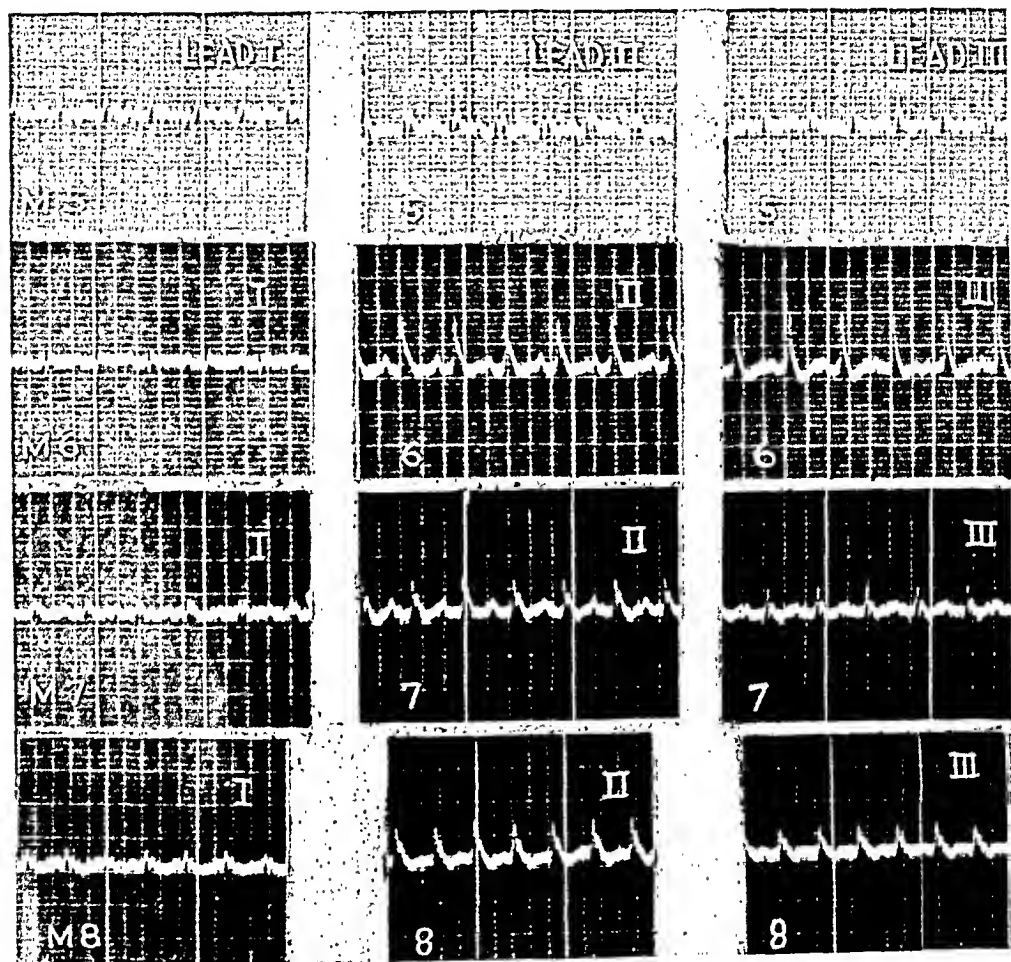


Fig. 2.—Typical appearance of four other white mouse electrocardiograms obtained with an Einthoven string galvanometer electrocardiograph. The film speed is 75 mm. per second, the fine time lines are spaced 0.04 second, and the heavy time lines are spaced 0.20 second. The string speed is approximately 0.01 second.

A galvanometer which produces a standardization curve such as that in Fig. 4, *A*, with angles *ABC*, *BCD*, *CDE*, and *DEF* perfect right angles, is capable of registering high speed (short duration) and low speed (long duration) electrical phenomena with no discrimination. The instantaneous response of the galvanometer (in zero time) to the standardizing potential indicates that the galvanometer is capable of following the fastest waves without introducing distortion. Since the beam remains parallel to the isoelectric line while the millivolt is applied, extremely slow electrical phenomena may likewise be regis-

tered without distortion. All intermediate electrical waves must, accordingly, be accurately recorded.

The Einthoven String Electrocardiograph.—An Einthoven string galvanometer electrocardiograph does not reproduce the theoretically perfect standardization curve under normal operating conditions. Any moving mass (such as a string) requires a definite amount of time to travel the distance BC or DE (Fig. 4, A). An Einthoven string electrocardiograph under normal operating conditions registers a standardization curve similar to Fig. 4, B. Angles ABC, BCD, CDE, and DEF are not right angles because the galvanometer beam consumes time t in traversing the distance BC or DE.

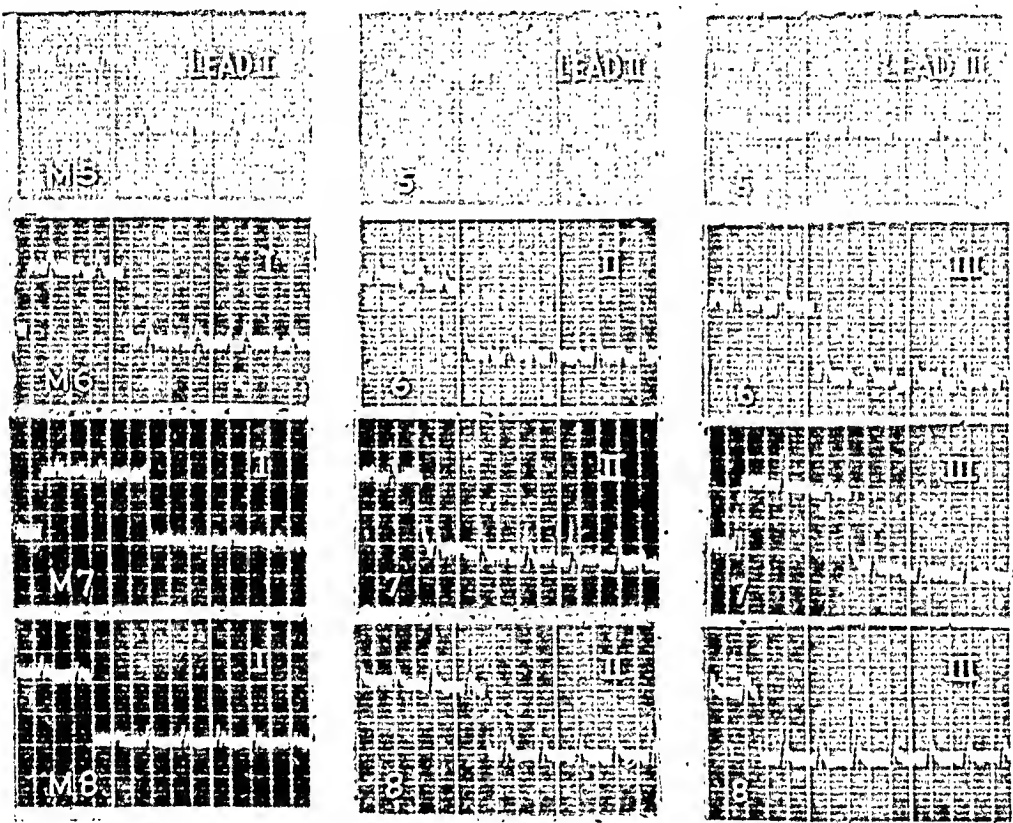


Fig. 3.—Electrocardiograms which illustrate how the white mouse electrocardiographic configuration is altered at high galvanometric speed as compared to the usual electrocardiographic string speeds. The records of Fig. 3 were taken on the same mice as those of Fig. 2. The high and low speed records on each mouse were taken within a few minutes of each other. The string speed is approximately 0.0015 second.

In an Einthoven galvanometer, the string tension is adjustable. The more taut the string, the higher is the natural vibratory period. A string of higher natural period consumes less time in traversing the distance BC or DE (Fig. 4, B) than at a lower natural period. Thus, as the string is drawn taut, the standardization curve approaches more closely the theoretically perfect curve of Fig. 4, A.

When the string tension is increased, the sensitivity is decreased; all Einthoven string electrocardiographs employ this principle for sensitivity control. Also, as the string tension is increased, the speed of the string is increased. Therefore, when an electrocardiograph is standardized so that a one centimeter deflection occurs when a millivolt is applied to the patient-galvanometer circuit, the tension of the string is thereby automatically selected. The constants of the galvanometer plus the resistance of the subject predetermine the speed of the string for a fixed value of sensitivity. An average commercial Einthoven string electrocardiograph, to which a subject with a "patient resistance" of about 2,000 ohms is connected, possesses a string speed of approximately 0.01 second. That is, the time t of Fig. 4, B is equal to approximately 0.01 second.

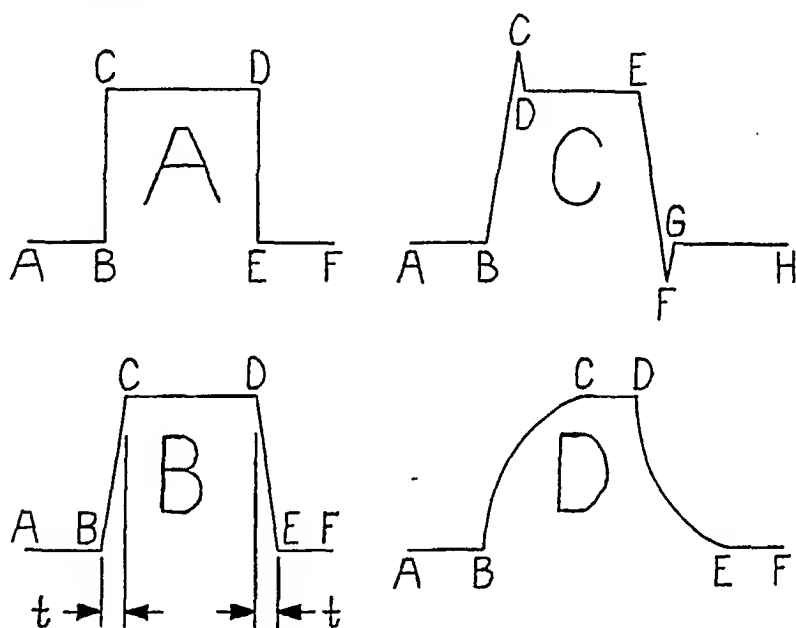


Fig. 4.—Einthoven string galvanometer standardization pulses.

The speed of an Einthoven string is directly dependent upon the resistance of the subject connected to it. When the subject resistance is more than 2,000 ohms, the string requires a time interval greater than 0.01 second to traverse the distance BC (Fig. 4, B). In man, a "patient resistance" of 2,000 ohms is a reasonable average value. Seldom does it fall below about 1,000 ohms, and, in some persons, a "patient resistance" of several thousand ohms is not uncommon. In small animals, the resistance is usually well in excess of 2,000 ohms unless extreme care is taken to keep the resistance low.

A factor of utmost importance is the degree of damping to which the string is subjected. In Fig. 4, A or Fig. 4, B, when the millivolt was applied at point B, the string traveled the one centimeter distance BC and came to a stop at C. All strings possess a definite mass, and, when set in motion, tend to remain so even after the activating stim-

ulus is removed. Unless something intervenes to prevent the string from overshooting its point of destination, a standardization curve such as that in Fig. 4, *C* is registered.

In commercial string electrocardiographs which employ a circuit resistance of a few thousand ohms (resistance of string plus "patient resistance"), overshooting at normal string tension is prevented by air friction, and, to a slight degree, by electromagnetic damping.³ The effectiveness of electromagnetic damping as compared to air friction damping is so small that the former may be omitted in this discussion. The Einthoven galvanometer for electrocardiographic application must be so designed that at normal sensitivity (1 centimeter deflection per millivolt), with a "patient resistance" of approximately 2,000 ohms, the adjustment of the string is such that no overshooting takes place, and the string speed is approximately 0.01 second, or faster. This condition of damping must be fulfilled over a considerable range of string tension (above and below the optimum resonance value) for minimal distortion.

When a subject with a "patient resistance" considerably higher than 2,000 ohms is connected to the electrocardiograph, the string must be slackened to obtain the standard sensitivity of one centimeter deflection per millivolt. As a result, the speed of the string is decreased but the air friction is unaltered. The amount of air friction required to bring a loose string to a stop is less than for a taut string; this may result in an overdamped standardization curve (Fig. 4, *D*).

Electrocardiograms obtained with apparatus which produces standardization curves which are underdamped or overdamped are very likely distorted. Overshooting or underdamping tends to distort the electrocardiogram by increasing the amplitude of the fast initial deflections. Overdamping tends to decrease the amplitude of the fast deflections and slurs the faster electrocardiographic waves.

A standardization curve of any Einthoven string electrocardiograph indicates whether the apparatus is capable of registering an electrocardiogram accurately if:

1. The damping is critical; more than slight overdamping or underdamping is not permissible.
2. The string speed is not slower than 0.02 second (after Lewis and Gilder⁴ for *human electrocardiographic applications*).
3. During the application of the standardization pulse of one millivolt, the string shadow deflects and remains deflected one centimeter.

Another source of distortion when the Einthoven string electrocardiograph is used is polarization effects⁵ if improper electrode technique is employed. The distortion caused by polarization appears in a form similar to that of the underdamped string or overshooting.

The Electronic Booster.—The galvanometric speed of an Einthoven string electrocardiograph is limited. Slight improvements may be made by increasing the optical magnification and the magnetic field strength and by modifying a few other galvanometric factors. The loss of photographic definition and the disproportionate increase in the size of the magnetic structure which inevitably result from such procedure is definitely not compensated for by the slight gain in string speed.

When a galvanometric speed much faster than 0.01 second is desired for electrocardiographic work, the most economical and simplest procedure is to employ an electronic booster, or amplifier, in conjunction with a high natural period galvanometer. The galvanometer may be in the form of an Einthoven galvanometer whose string is drawn very taut; a reduction in the string length also increases the natural period. To attain extremely high speeds, both procedures may be necessary.

High natural period, "moving coil," or "moving vane" galvanometers may be substituted for the Einthoven galvanometer if an electronic booster is employed; these galvanometers are commonly referred to as "mirror" or "rotating mirror" galvanometers.³ Most commercial amplifier electrocardiographs are of the "rotating mirror" variety. For the ultimate in galvanometric speed, the cathode ray oscillograph,³ which employs a moving beam of electrons, may be used.

Two types of electronic amplifiers may be employed for electrocardiographic purposes, namely, the resistance-capacity coupled, and the direct coupled.⁶ In a direct coupled amplifier, the electrical waves during the process of amplification pass through resistances and electronic tubes only. In the resistance-capacity coupled amplifier, the electrical waves pass through resistances, condensers, and electronic tubes. When a direct coupled amplifier is used, the operating characteristics of the electrocardiographic system are identical with that of the Einthoven system except that the galvanometric speed may be made much higher. The direct coupled amplifier may be considered as an adjunct to the optical system and the magnetic structure of the galvanometer, i.e., as an electronic magnifier for obtaining greater sensitivity to compensate for the loss in sensitivity when the galvanometric speed is increased.

A detailed technical discussion of direct coupled amplifiers which are suitable as electrocardiographic boosters is somewhat beyond the scope of this paper. It should, however, be mentioned that a direct coupled amplifier electrocardiograph is capable of producing a standardization curve similar to that of Fig. 4, *B*. The time element t may be considerably reduced by using either a fast Einthoven string galvanometer or a high natural period "mirror" galvanometer. The effects of "patient resistance" are eliminated for reasons which will be discussed later. Skin currents or potentials must be compensated for as is done in an Einthoven string electrocardiograph.

A reason for not using the direct coupled booster for electrocardiographic work is its characteristic instability. Direct coupled amplifiers with sufficient sensitivity to respond to one millivolt impulses usually exhibit this property. The resistance-capacity coupled amplifier, on the other hand, is a stable and reliable device, but possesses certain inherent characteristics which are somewhat different from that of the direct coupled amplifier and Einthoven string electrocardiograph. These dissimilar characteristics, however, are not a detriment, but a decided electrocardiographic asset, if properly controlled.

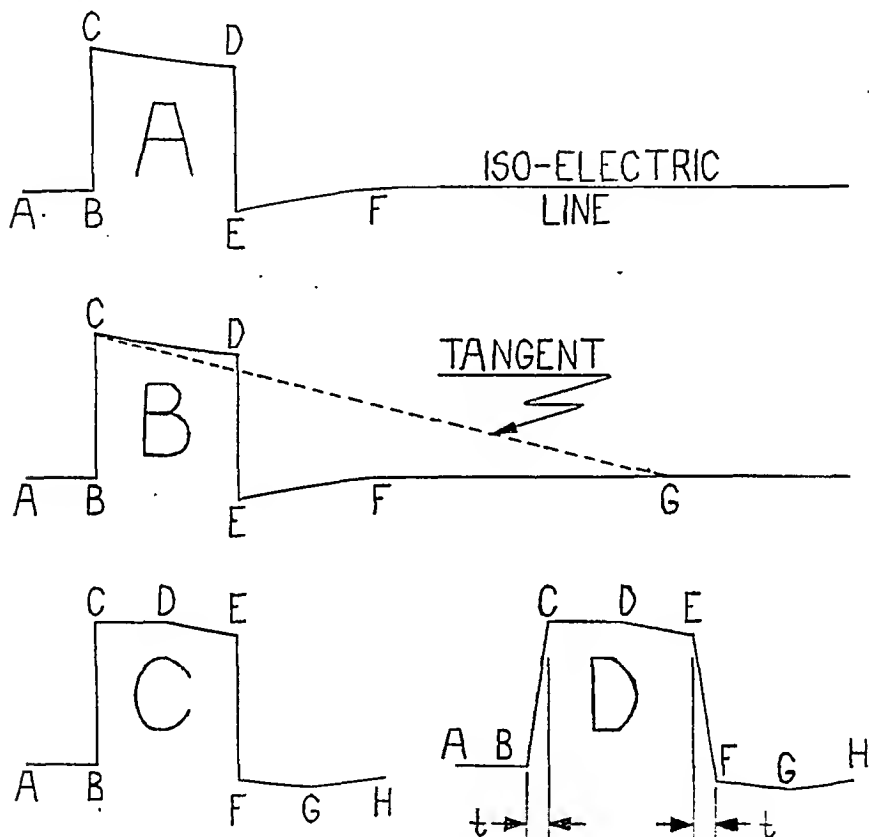


Fig. 5.—Resistance-capacity coupled amplifier standardization pulses.

If an infinitely fast galvanometer could be constructed which consumed zero time in traversing one centimeter when a millivolt was applied, and if the galvanometer were driven by a resistance-capacity coupled amplifier, a standardization curve similar to that shown in Fig. 5, A would be registered. AB represents the isoelectric line. At point B the millivolt standardizing potential is applied and the galvanometer deflects one centimeter in zero time to point C. From point C, the standardization is unlike that of an Einthoven string electrocardiograph in that the galvanometer beam does not remain one centimeter above the isoelectric line but tends to approach it at a logarithmic rate. That is, if the millivolt is applied for a considerable period, the galvanometer beam eventually drops to the level of the isoelectric line.

The logarithmic decrement is caused by the resistance-capacity coupled amplifier. In this type of amplifier, when the millivolt is applied, the condensers in the circuit become charged and then discharge through the associated resistors. The rate of decay may be controlled by means of the resistors and condensers. The larger the resistors and condensers, the slower is the rate of decay.

When the millivolt is removed at point D, the galvanometer beam drops exactly one centimeter below point D to point E, which is somewhat below the isoelectric line. The distance point E falls below the isoelectric line depends upon the time of application of the millivolt, as is obvious from the figure. From point E, the beam gradually drifts back to the level of the isoelectric line. Line EF is also logarithmic and similar to line CD.

Schwartzchild and Kissin⁷ ascertained the relationship of decay rate to electrocardiographic accuracy. They found that if a tangent CG is drawn (Fig. 5, B) to the logarithmic decrement CD at point C, and if the duration of BG is two seconds or more, the apparatus is suitable for clinical purposes. Theoretically, the greater the duration of BG, the more accurate is the electrocardiograph in the registration of low frequency or slow cardiac changes.

Miller,⁸ by a modification of the electronic circuit, succeeded in producing a standardization curve which resembles that of Fig. 5, C. After the initial millivolt deflection, the beam is parallel to the isoelectric line for approximately 0.1 to 0.2 second (represented by CD), and then commences to decay logarithmically to point E, where the millivolt is removed. The beam immediately deflects one centimeter (represented by EF). Point F falls below the isoelectric level a distance equal to the logarithmic decay that has taken place (represented by DE). FG is a continuation of the logarithmic curve DE, but displaced one centimeter. At point G the beam commences to return to the isoelectric level. If the millivolt were removed before point D was reached, no logarithmic decay would have taken place. In such a case, the beam would drop exactly to the isoelectric line.

The purpose of the Miller circuit is to reproduce the Einthoven string electrocardiograph type of standardization and retain the advantages of the resistance-capacity coupled amplifier. For a period of about 0.1 to 0.2 second after the millivolt is applied, conditions are exactly similar to that of the Einthoven string electrocardiograph for the registration of slow phenomena. There is no known electrocardiographic wave which has a constant potential duration in excess of 0.1 second. Therefore, any slow electrocardiographic wave must register accurately when the standardization possesses a flat top for a period of 0.1 second or more.

As in the Einthoven string electrocardiograph, the moving element of the galvanometer requires a definite amount of time to traverse the one centimeter when a millivolt is applied. Therefore, the actual standardization should appear as in Fig. 5, D, where the deflection time

through the string; a decrease in cardiac current flow through the string in turn produces a proportionate decrease in string deflection. Thus, with a 2,000 ohm string and a possible difference of several hundred ohms between leads, the percentage change in electrocardiographic sensitivity may be considerable. For example, if the "patient resistance" is 2,000 ohms, the string resistance is 2,000 ohms, and the instantaneous cardiac action potential is one millivolt, the instantaneous current through the string, according to Ohm's law, is

$$\frac{0.001}{2,000 + 2,000} = 0.25 \text{ microampere.}$$

Should the "patient resistance" in another lead be 4,000 ohms, the instantaneous current in the string would be

$$\frac{0.001}{4,000 + 2,000} = 0.16 \text{ microampere.}$$

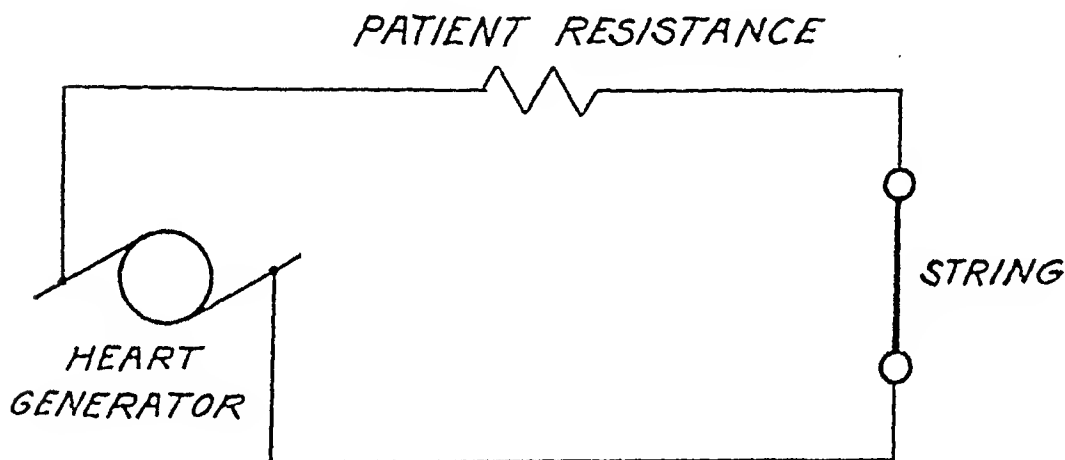


Fig. 6.—Schematic of electrical components to illustrate the relationship of the heart as a generator, and the consideration that must be given the "patient resistance" and the "string resistance."

If the string was adjusted to deflect one centimeter per millivolt with the 2,000 ohm lead, as is normally done in electrocardiography, the substitution of a 4,000 ohm lead would produce a deflection of 0.64 centimeter instead of the required one centimeter. To compensate for the loss in sensitivity in the latter lead, the string must be made more slack.

In an amplifier electrocardiograph (direct coupled or resistance-capacity coupled), the patient is connected across a resistance in the grid circuit of the amplifier (Fig. 7). The grid resistor may possess a value of several million ohms. If we apply Ohm's law to the resulting patient circuit, we find that, with a 2,000-ohm patient, a 10 million ohm grid resistor, and an instantaneous cardiac action potential of one millivolt, the instantaneous current which flows through the grid re-

sistor is $\frac{0.001}{2,000 + 10,000,000}$ ampere, whereas, with a 4,000 ohm patient, the instantaneous current is $\frac{0.001}{4,000 + 10,000,000}$ ampere. The

amount of current that flows through the grid resistor controls the deflection of the electrocardiographic beam for a fixed setting of the sensitivity control. Therefore, a difference of several thousand ohms in "patient resistance" can merely alter the current through the grid resistor by an insignificant percentage for equal values of instantaneous cardiac potential. Therein lies the reason why an amplifier type electrocardiograph with a high input resistance may be standardized initially and any combination of leads registered thereafter without readjusting the sensitivity.

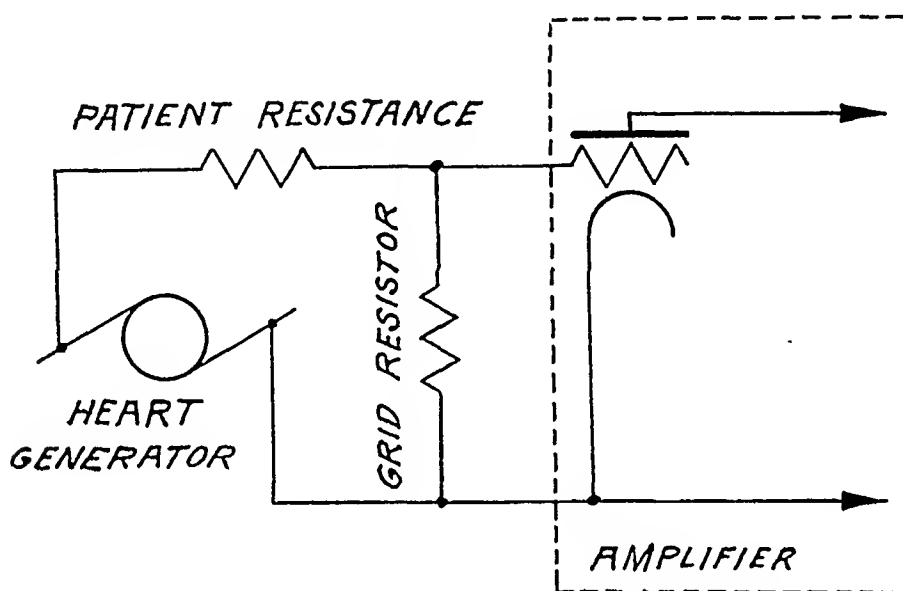


Fig. 7.—Schematic of the input circuit of an amplifier electrocardiograph.

In an electronic electrocardiograph, the speed of the galvanometer may be permanently set. Unlike the Einthoven electrocardiograph, in which the sensitivity is controlled by adjusting the string tension, and, in turn, the string speed, the sensitivity of the electronic electrocardiograph is adjusted by means of a control in the amplifier which adjusts the degree of amplification, and, in turn, only the electrocardiographic sensitivity. As a result, the characteristics of the galvanometer in the electronic electrocardiograph are unaltered under all possible sensitivity settings.

The Experimental Apparatus.—Fig. 8 shows the electrical circuit of the resistance-capacity coupled amplifier which was used in conjunction with an Einthoven string electrocardiograph. By varying the string tension, the galvanometric speed was adjustable between the limits of less than 0.01 second and approximately 0.0015 second.

A description of the booster follows: A standard three limb patient cable such as is used on all electrocardiographs connects with a lead selector switch with four positions: Standardize, and Leads I, II, and III. The lead selector switch is followed by a three stage

resistance-capacity coupled amplifier. The first and second stages are triodes contained in the type '19 tube; the third stage is a 1S5 tube wired as a triode. Between the third stage and the Einthoven string electrocardiograph is an equalizing circuit to critically damp the string. That is, when a string is drawn more taut than the customary electrocardiographic tension, air friction damping is inadequate to prevent the string from overshooting. As a result, an equalizing circuit must be added. The Miller corrective network for producing a flat top standardization is located in the plate circuit of the second stage. The standardization circuit for producing a millivolt pulse is located at the input of the amplifier, i.e., between the lead selector switch and the grid circuit of the first stage.

When constructing the resistance-capacity coupled booster, the following should be kept in mind:

1. In the Miller corrective network, the 0.45 megohm resistor may have to be varied slightly in order to obtain the flat top standardization curve. Once this adjustment is made, it does not have to be altered during the life of the apparatus.

2. If string speeds well in excess of 0.0015 second are desired, the equalizing circuit shown in Fig. 8 may be inadequate; in such a case, a resonant shunt damping circuit³ must be substituted.

3. In the standardization circuit, an ordinary 1.5 volt dry cell may be used. Because the drain is negligible, and lasts only for very short periods, while the millivolt switch is depressed, the cell will maintain its voltage within electrocardiographic measuring accuracy for at least six months of its shelf life. The voltmeter indicates whether the voltage of the cell is within required limits.

4. The entire amplifier, plus batteries, must be built into a metal case to eliminate the possible pickup of stray alternating current disturbances. The metal case must be electrically connected to the magnet structure or ground circuit of the Einthoven string electrocardiograph.

5. It is advisable to support the amplifier unit on soft rubber pads in order to eliminate mechanical disturbances.

6. String centering and protection are accomplished by means of the usual controls in the Einthoven electrocardiograph.

Technique.—The unanesthetized mouse is tied in a supine position to a board (Fig. 9). The same procedure is also applicable to the larger laboratory animals. The four paws are first tied to the nails on the wood block. Electrode jelly is then applied to the right and left fore paws and the left hind paw. The electrode consists merely of a fine copper wire twisted around the paws (approximately four turns) over the areas to which the electrode jelly had been applied. (In some instances, pin electrodes were used instead of the jelly and wire.) The patient cable of the amplifier is then connected to the spring clips so that the "right arm" corresponds to the right fore

paw, the "left arm" to the left fore paw, and "left leg" to the left hind paw.

Subject resistance does not affect the accuracy of the electrocardiogram when an amplifier type electrocardiograph is used. However, the higher the subject resistance, the greater is the likelihood of picking up alternating current disturbances of an electrostatic nature.

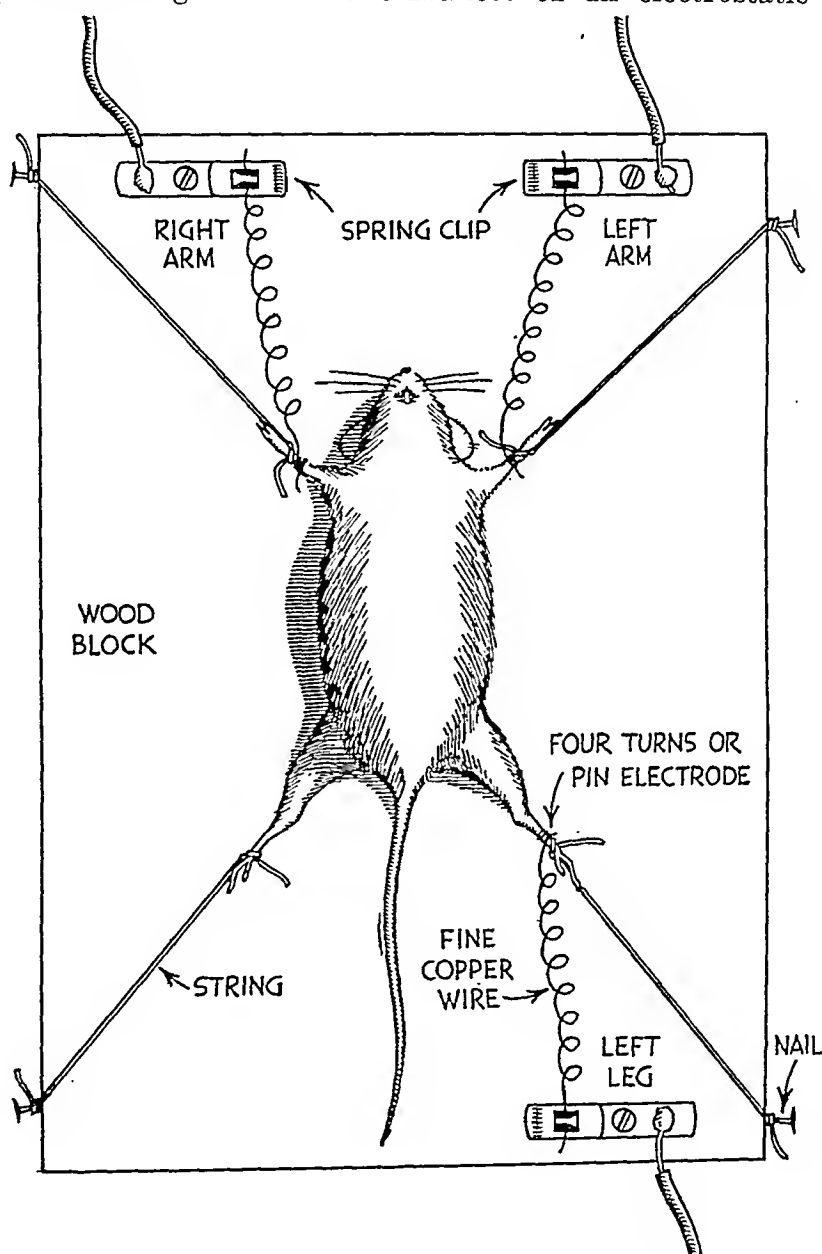


Fig. 9.—Diagram showing manner in which a small animal, such as a mouse, may be connected to an electrocardiograph.

Therefore, in locations where alternating current wiring and apparatus are present, more care should be taken to keep the subject resistance low.

Recordings of the three standard leads were taken both with and without the amplifier. The interval between the two sets of recordings

was very short, i.e., merely the time required to make the necessary adjustments. The animal during this interval was not disturbed.

We found that it is generally desirable to allow the animal to remain in position and undisturbed for several minutes after all adjustments are made to it before registering the electrocardiogram. As a general rule, the animal will quiet down sufficiently to allow the taking of satisfactory electrocardiograms. After mice have been subjected to this treatment several times, they become less excitable and more cooperative.

Electrocardiographic Observations.—Seldom are white mouse electrocardiograms completely free of somatic tremor when taken with an electrocardiograph which possesses a high galvanometric speed, although the mouse may have appeared relaxed; at usual galvanometric speeds, the electrocardiograms are usually free of somatic tremor when the same technique is used. As the galvanometric speed is gradually increased, the presence of somatic tremor in the electrocardiogram becomes more evident. This indicates that somatic tremor in a mouse is of a comparatively high frequency. As the galvanometric sensitivity to the higher frequencies is increased, the somatic tremor components register with increased amplitude. The frequency of the major components of the tremor lies between approximately 200 and 1,000 cycles per second.

When white mouse electrocardiograms are taken at the usual galvanometric speeds of approximately 0.01 second (Figs. 1 and 2), they show a distinct P wave. The QR interval is usually less than the galvanometric speed. What appears to be the RS interval is, as a general rule notched; below the notch, the complex appears slurred. No T wave is seen. The electrocardiogram, as a whole, does not resemble those from larger animals.

On the other hand, when high galvanometric speeds of 0.0015 second or more are employed on the same mice (Fig. 3), the electrocardiogram does resemble that of a larger animal in many respects. A P wave is present. The QR interval is of longer duration than the galvanometric speed. A distinct and normal appearing QRS complex is present. A distinct S wave is present in at least one of the three leads of each mouse. The T wave occurs rather soon after the S wave, and in most normal mice it appears in continuity with the S wave.

The average commercial electrocardiograph is designed primarily for human application. In small animal work the electrocardiographic requirements are more exacting because of the high cardiac rates and short duration of some of the complexes. Thus, when an electrocardiogram is taken with an average commercial electrocardiograph which possesses a galvanometric speed not much in excess of 0.01 second, several forms of distortion may be introduced.

The most obvious electrocardiographic distortion in the white mouse is in the general appearance of the QRS and T waves. As was previ-

ously mentioned, if the galvanometric speed is slower than the electrical phenomenon that is being graphically recorded, the electrical phenomenon will register inaccurately. The duration of the QR interval in the average normal mouse is considerably less than 0.01 second. As a result, the graphic representation of the QR segment is incorrect in a slow system. Also, the cardiac action potential which stimulates the galvanometer terminates before the galvanometer has had a chance to traverse the required distance. The result is an amplitude attenuation of the QRS registration.

Likewise, the RS segment is distorted if the galvanometric speed is too slow. That is, the electrocardiographic registration lags behind the action potential, and the action potential terminates before the recording beam or shadow has traversed the true distance. The T wave which follows immediately registers as a notch on the RS segment, well above the isoelectric line. The slurring effect is actually part of the T wave. The S wave must obviously be absent. Also, because the slopes of the fast waves are incorrectly registered, the duration of a fast wave, such as R, must register incorrectly.

Because of the fact that the electrocardiographic complexes do not register with the correct slope and amplitude when the galvanometric speed is too slow, phase distortion is introduced. That is, the time intervals between electrocardiographic complexes are reproduced incorrectly because the slow waves register correctly and the fast waves appear displaced from their true location.

SUMMARY AND CONCLUSIONS

1. A theoretically perfect galvanometer for electrocardiographic work produces a standardization wave which is a perfect rectangle. That is, zero time is consumed by the galvanometer in traversing the one centimeter deflection, and during the application of the millivolt the beam is parallel to the isoelectric line, but displaced one centimeter.

2. An Einthoven string galvanometer electrocardiograph cannot reproduce the theoretically perfect standardization curve because any moving mass, such as a string, requires a definite amount of time to traverse the one centimeter distance when the millivolt is applied. The resultant standardization curve must therefore resemble a trapezoid.

3. In an Einthoven galvanometer, the string tension is adjustable. The more taut the string, the higher is its natural vibratory period. A string of higher natural period consumes less time in traversing the one centimeter distance when the millivolt standardizing pulse is applied than one with a lower natural period.

4. When the string tension is increased, the sensitivity is decreased; all Einthoven string electrocardiographs employ this principle for sensitivity control. Also, as the string tension is increased, the speed of the string is increased. Therefore, when an electrocardiograph is standardized so that a one centimeter deflection occurs when a milli-

volt is applied, the tension of the string is automatically selected. The constants of the galvanometer plus the resistance of the subject predetermine the speed of the string for a fixed value of sensitivity.

5. A factor of utmost importance is the degree of damping to which the string is subjected. Overdamping or underdamping tends to distort the electrocardiogram.

6. The standardization curve of any Einthoven string electrocardiograph indicates whether the apparatus is capable of registering an electrocardiogram accurately.

7. Electrocardiographic distortion caused by polarization effects may occur if improper electrode technique is employed.

8. The galvanometric speed of an Einthoven string electrocardiograph is limited. When a galvanometric speed much faster than about 0.01 second is desired for electrocardiographic work, the most economical and simplest procedure is to employ an electronic booster or amplifier in conjunction with a high natural period galvanometer.

9. Two types of electronic amplifiers may be employed for electrocardiographic purposes, namely, the resistance-capacity coupled and the direct coupled. The resistance-capacity coupled amplifier is the better of the two.

10. The theoretically perfect standardization curve of a resistance-capacity coupled amplifier type electrocardiograph is not exactly similar to that of the theoretically perfect Einthoven electrocardiograph. For approximately the first 0.1 to 0.2 second after the millivolt is applied, conditions are exactly similar to the Einthoven system, but, thereafter, a logarithmic decrement sets in until the beam reaches the isoelectric line.

11. Although the theoretically perfect condition, under which the beam will deflect one centimeter in zero time when a millivolt is applied, cannot be achieved even with an amplifier type electrocardiograph, this perfect condition may be approached more closely.

12. As the galvanometric speed is increased, the amplifier must be made more powerful and, in turn, more costly. From an economic standpoint, it is not preferable to employ galvanometric speeds in excess of electrocardiographic requirements.

13. A galvanometric speed of approximately 0.0015 second is ample for registering the fastest electrocardiographic complexes that may be found in a mammal as small as the white mouse, whose average normal heart rate is approximately 750 beats per minute.

14. A resistance-capacity coupled amplifier type electrocardiograph is capable of automatically compensating the subject's skin potentials. An Einthoven string electrocardiograph requires a manually operated compensation control. The logarithmic decay characteristic which is common to all resistance-capacity coupled amplifier electrocardiographs accomplishes the automatic skin potential compensation.

15. When an electrocardiogram is taken with an Einthoven string electrocardiograph, the machine must be recalibrated for each lead; the amplifier coupled electrocardiograph does not require recalibration with each lead.

16. In an electronic electrocardiograph the speed of the galvanometer may be permanently set. Unlike the Einthoven electrocardiograph, in which the sensitivity is controlled by adjusting the string tension and, in turn, the string speed, the sensitivity of the electronic electrocardiograph is adjusted by means of a control in the amplifier which adjusts the degree of amplification and, in turn, only the electrocardiographic sensitivity.

17. The constructional features of a resistance-capacity coupled amplifier that may be used with a commercial Einthoven string electrocardiograph for small animal work are given.

18. The technique for small animal electrocardiography is described.

19. The theoretical aspects of distortion in small animal electrocardiography are discussed. Experimental proof is given that average commercial electrocardiographs (both Einthoven string and amplifier types) are incapable of registering the cardiac action potentials of small animals with any degree of accuracy. Commercial electrocardiographs are designed primarily for human application, where the requirements are not so severe.

20. The accurate recording of electrocardiographic complexes, as described herein, makes possible further investigations in which electrocardiographic principles may be applied in small animal experimentation.

We wish to express our appreciation for the cooperation of the Sanborn Company, of Cambridge, Massachusetts, in this investigation. We are also grateful for the constructive criticisms of Dr. Paul D. White, of the Massachusetts General Hospital.

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THE PROGNOSTIC SIGNIFICANCE OF AGE AT ONSET IN INITIAL ATTACKS OF RHEUMATIC FEVER

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ALTHOUGH there is difference of opinion regarding the seriousness of the prognosis in rheumatic fever at different ages within childhood,¹⁻⁴ it is generally accepted that the disease is more serious and more likely to lead to cardiac damage in children than in adults. This conclusion has had support from a number of investigations, most of which have been based on long-term observations on groups of patients over a number of years. Obviously, however, estimation of the significance of age at onset in these long-term studies is complicated by the important fact that repeated attacks have occurred in many of the patients but not in others. This difficulty can be obviated by limiting one's analysis to the results of initial attacks only, and this has been done by several observers. Church,⁵ in a study of 244 first attacks, found that 75 per cent of the patients under 10 years of age developed signs of cardiac damage, but that this figure diminished progressively to 12.5 per cent in those who developed first attacks after 40 years of age. Maekie⁶ found cardiac involvement in 74 per cent of 112 patients under 15 years of age, and in 38.3 per cent of 107 patients over 25 years of age. Similar differences between children and adults with initial attacks of rheumatic fever were reported from Australia by Sangster,⁷ who found persisting evidence of cardiac damage at the time of discharge from the hospital in 40 per cent of children under 12 years of age and in 25 per cent of patients over that age. Reports limited to children have been made by Sutton and Dodge⁸ and Ash.⁹ The former studied 66 children in their first attacks of rheumatic polyarthritis, and noted carditis in 40.9 per cent and persisting evidence of heart disease at the time of discharge from the hospital in 27.3 per cent. In Ash's group of 297 children with polyarthritis, 60 per cent were considered to have organic valvular disease at the termination of the initial attack.

In studying the incidence of cardiac damage in rheumatic fever one is interested in knowing, first, whether the heart is involved during the attack, and, second, whether the damage resulting from that involvement is sufficient to cause clinically recognizable, persistent, organic heart disease. In none of the reports mentioned above were both of these analyzed for both children and adults, and this study was undertaken for that purpose.

All patients studied were from the Third (New York University)

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Medical Division and the Children's Medical Service* of Bellevue Hospital. The cases reviewed from the adult service covered the period 1920 to 1937, and those from the children's service, the period 1930 to 1937. The children were 12 years old or less, and the adults over 25 years; the interval from 12 to 25 years was omitted in order to insure a distinct separation of the two groups. Originally, we had intended to include all types of rheumatic manifestations in the analysis, but chorea and carditis without joint involvement were so infrequently encountered during first attacks in the adults that polyarthritis was the only manifestation which could be used for comparison of the two age groups.

Cardiac damage was divided into the two categories previously mentioned: (1) carditis during the attack of rheumatic fever, and (2) the development of pathologic changes in the heart sufficient to lead to signs of persisting organic heart disease at the termination of the rheumatic activity. The criteria for making a diagnosis of carditis were the appearance while under observation of one or several of the following in a patient with rheumatic fever: (1) Diastolic murmurs with or without cardiac enlargement, or systolic murmurs with enlargement, (2) significant electrocardiographic changes,† (3) gallop,‡ (4) precordial pain and tenderness, (5) significant arrhythmias, (6) disproportionate tachycardia,‡ and (7) pericardial friction rub or effusion. The criteria for persisting organic heart disease were the presence of diastolic murmurs or of systolic murmurs plus cardiac enlargement at the time of discharge from the hospital, after all evidence of active carditis and all other manifestations of active rheumatic fever had disappeared. To insure accuracy of interpretation, all patients with an unreliable or uncertain previous history or with indications of possible cardiac involvement prior to admission were excluded. Because of the strictness of the requirements, it is probable that some cases of mild rheumatic fever with low-grade carditis which could not be diagnosed with certainty were excluded. However, by employing uniform criteria for the inclusion of adults and children we believe that accurate comparisons have been attained.

RESULTS

The results of this comparison are shown in Table I. Of 67 adults with an initial attack of frank polyarthritis, 30 per cent developed cardi-

TABLE I

CARDIAC DAMAGE IN CHILDREN AND ADULTS WITH INITIAL ATTACKS OF RHEUMATIC POLYARTHRITIS

AGE	NUMBER OF PATIENTS	INCIDENCE OF CARDITIS		INCIDENCE OF PERSISTING CARDIAC DAMAGE	
		NUMBER	PER CENT	NUMBER	PER CENT
Under 12 years	78	36	46	22	28
Over 25 years	67	20	30	5	7

*Many of the children had been included in the report of Sutton and Dodge.⁸

†In addition to the frank arrhythmias, the changes accepted as significant were prolongation of the P-R interval and the changes associated with pericarditis.

‡These were accepted as indicative of carditis only when accompanied by other signs.

cluded, the mortality rose to 3.6 per cent. Among the 78 children with polyarthritis, one (1.3 per cent) died; whereas, among twelve who had subcutaneous nodules, three (25 per cent) died. This high mortality in the children with nodules is in agreement with the accepted view regarding their serious prognostic significance, but in this connection it must be noted that three of the surviving children with nodules left the hospital with no physical signs of cardiac damage, although they did have carditis during the height of the illness. Of course, severe carditis was present in all the fatal cases. These figures are in conformity with the usual clinical opinion regarding fatality in initial attacks of rheumatic fever.

Finally, it must be emphasized that the relatively low incidence of serious cardiac damage suffered by the adults of our series does not warrant a lessening of vigilance in the care of this age group. This is especially true in the case of adults whose hearts have already sustained damage in earlier attacks of rheumatic fever, for it is our belief that in these patients further cardiac damage almost invariably results.

SUMMARY

A clinical analysis was made of the incidence of cardiac damage during initial attacks of rheumatic fever. The data presented indicate that first attacks of rheumatic polyarthritis are less likely to be accompanied by clinically evident carditis in adults than in children, and that when carditis does occur it is very much less likely to result in serious cardiac damage in the adults.

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THE TONGUE SIGN FOR HIGH VENOUS PRESSURE

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THE veins of the undersurface of the tongue are admirably situated for observation. In the average person they are 8 inches, or 200 mm., above the right auricle, so that when the person is erect, or sitting, the veins are collapsed unless the venous pressure is abnormally high, i.e., greater than 8 inches, or 200 mm. Normal venous pressure is 50 to 150 mm., or 3 to 5 inches, so that the level of the tongue veins is just in the region of elevated venous pressure.

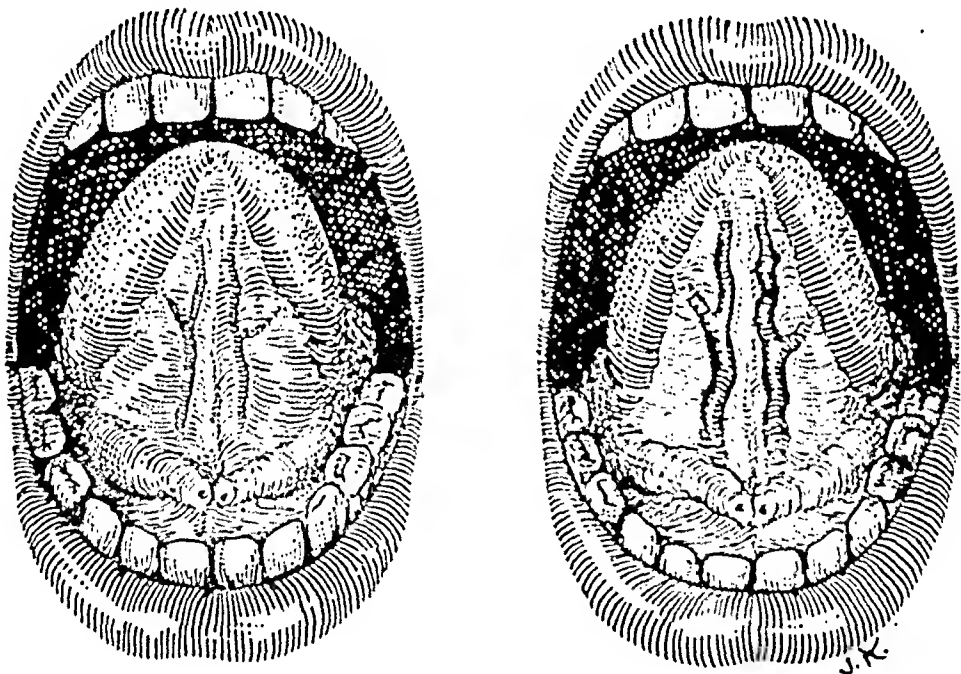


Fig. 1.

Clinically, we have found that this is a reliable sign of increased venous pressure, and one that is immediately obvious and certain. The dilation of the veins is unmistakable, and may be duplicated in the normal person by having him recline on a bed or couch.

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Clinical Reports

THE PHONOCARDIOGRAM IN SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE MEDIASTINUM

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THE sounds produced over the upper part of the precordium by spontaneous interstitial emphysema of the mediastinum and lung have intrigued the medical profession. Griffin¹ regards these "popping" or "crunching" sounds as diagnostic of this condition, and reported three cases with this sole thought in mind. Hamman,² who was the first to describe the condition (1937), also thought that these interesting physical signs are pathognomonic. The reports that followed Hamman's article³ applied a variety of descriptive terms to the precordial sounds; bubbling, crunching, popping, and crackling were those most frequently employed. The following case is reported because of the interesting phonocardiograms which were taken shortly after the occurrence of spontaneous mediastinal emphysema. To our knowledge, it is the first phonocardiogram in this condition to be reported.

REPORT OF A CASE

C. F., a 28-year-old white man, was admitted to Cedars of Lebanon Hospital Aug. 14, 1942, with a complaint of severe substernal pain of one and one-half hours' duration. The patient was an employee of the hospital ambulance company, and his work entailed lifting three to five patients a day. He was in excellent health until approximately ninety minutes before admission to the hospital, at which time, about an hour after having lifted a patient, he developed moderate substernal distress which radiated into his left arm to the elbow. He left his ambulance and helped lift another patient, but on the way to the hospital the pain became so severe that he told his partner he was afraid he could not help remove the patient. In about fifteen minutes the pain had attained terrific proportions, so that he lay back in his seat, became pale, and refused to move. Deep respirations were especially painful. He was seen shortly after arriving at the hospital. His blood pressure at that time was 130/90, his pulse rate, 90, and his respiratory rate, 30. Morphine sulfate in a dose of $\frac{1}{4}$ grain was given in the ambulance, and the man was removed to the ward.

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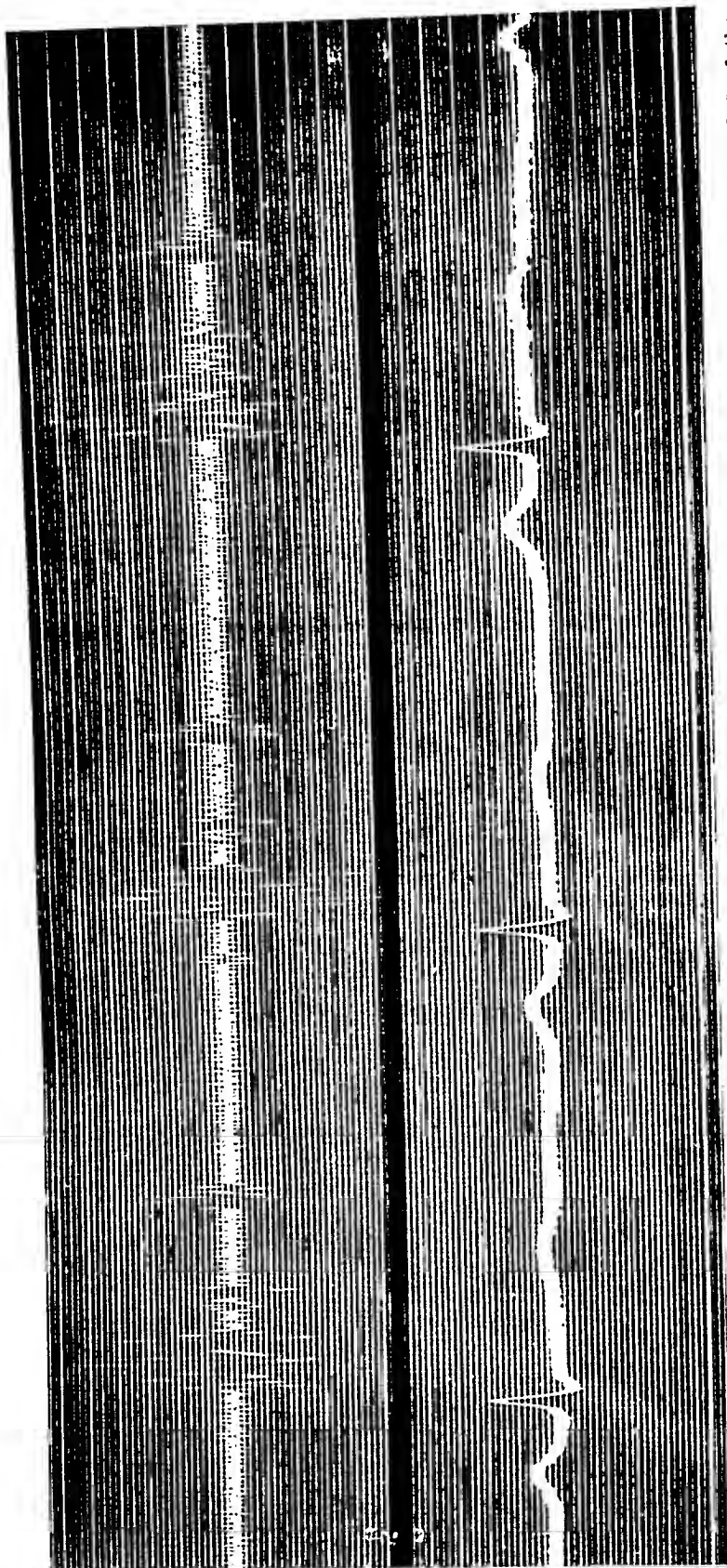


Fig. 1A.—Stethogram taken at the onset of the illness, over the precordium at the left parasternal line simultaneously with Lead I of the electrocardiogram. A large diaphragm bell was employed. Note the prolonged systole of varying intensity and pitch. There is also a slight presystolic bruit.

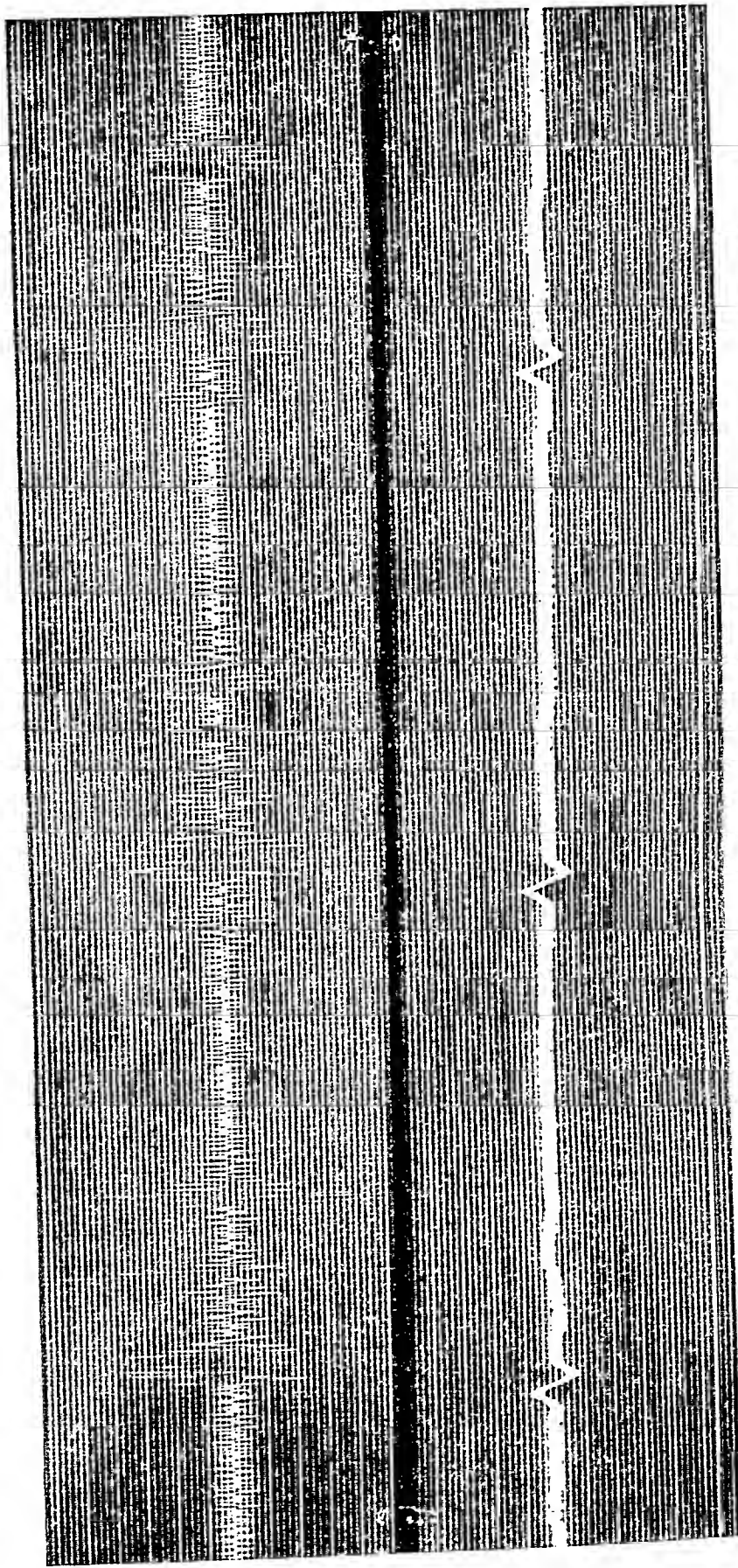


Fig. 1B.—Simultaneous electrocardiogram-stethogram taken in same area with Lead I and a large open bell.

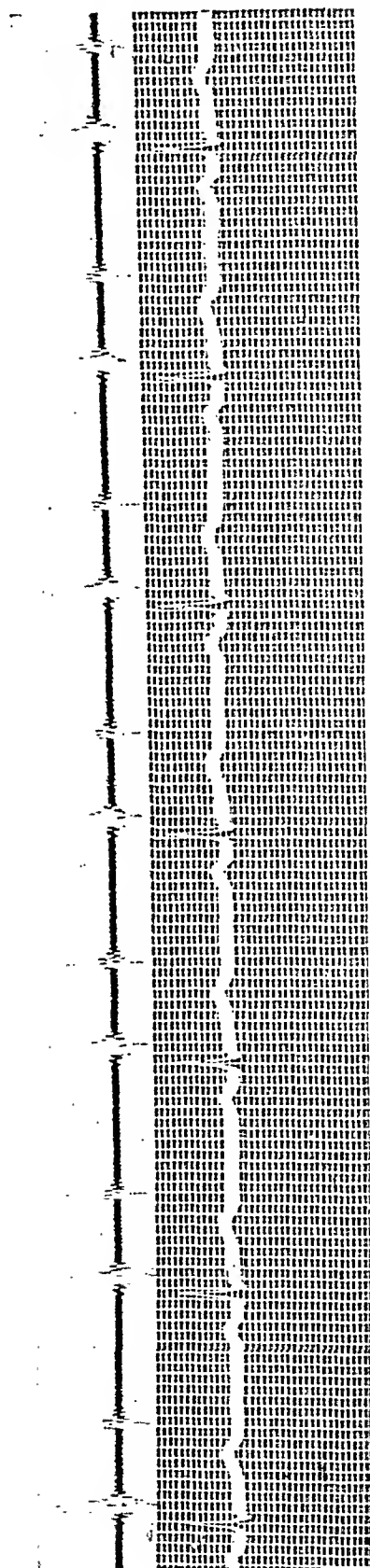


Fig. 2.—Simultaneous electrocardiogram-stethogram taken twelve days after the onset of the illness shows a return to normal.

Past History.—The patient had had inflammatory rheumatism at the age of 8 years. He was ill for one and one-half years at that time. His heart had been examined repeatedly thereafter, but no evidence of disease was reported. There was no history of tuberculosis or asthma. The family history was negative.

Physical examination revealed a white man who was lying comfortably in bed, smiling, and even laughing, and in no apparent distress—forty-five minutes to an hour after receiving $\frac{1}{4}$ grain of morphine sulfate. The blood pressure was 120/80, the pulse rate, 80, and the respiratory rate, 25 per minute. Physical examination was essentially negative except for the heart. There was resonance to 1 inch to the left of the sternum. Over the apex of the heart a remarkable sound was heard. It was a crunching, popping, knocking bruit, synchronous with the heart beat, and was heard best on deep expiration when the patient was lying on the left side. No subcutaneous emphysema developed. Expansion of the chest was limited, and the percussion note was not abnormal.

The hemoglobin was 96 per cent, the erythrocyte count, 5,000,300, and the leucocyte count, 9,500. The sedimentation rate was 12 mm. in 258 minutes. The blood Wassermann reaction was negative. The urine was normal. An electrocardiogram on August 14 showed an auricular and ventricular rate of 90, sinus rhythm, and normal A-V conduction time. Lead I showed low voltage of the R wave; Lead II showed low voltage of the QRS complex and upright T and P waves; Lead III showed low voltage of QRS, a small R wave, and an upright T wave; and Lead IV showed a small R wave and an upright T wave. A roentgenogram of the chest, August 14, showed that the heart was of comparatively normal shape, size, and position. The arch and descending aorta were also of normal shape and size. The hila were somewhat increased in size and density. The root branches were accentuated. There was a partial pneumothorax at the left apex. An electrocardiogram which was made August 17 was identical with that of August 14.

A phonocardiogram was taken on the day after admission and is reproduced in Figs. 1A, 1B, and 2. The pain decreased gradually. The day after admission he no longer needed opiates, his temperature varied between 97 and 98.8° F., his pulse rate remained constant between 70 and 80, and his respiratory rate was about 20. The precordial bruit decreased in intensity, and, on August 18, four days after its onset, it could scarcely be heard. The patient was always comfortable, and his only complaint after cessation of the sudden, severe pain on admission was that of discomfort on deep inspiration.

SUMMARY

A case of spontaneous mediastinal emphysema is reported. Phonocardiograms showed that the peculiar sounds produced by the air in the mediastinum were synchronous with each cardiac impulse and occurred regularly with each systolic contraction.

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ANEURYSM OF THE PULMONARY ARTERY

REPORT OF A CASE IN WHICH THE ANEURYSM APPARENTLY DEVELOPED
UNDER OBSERVATION

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ANEURYSM of the pulmonary artery is rare. According to Scott,¹ both Ambroise Paré and Lancisi observed cases. Boyd and McGavaek² reviewed the literature from 1833 to 1939, and discovered 111 cases in which the diagnosis was proved by autopsy. Since their paper was published, ten articles on the subject have been listed in the Quarterly Cumulative Index Medicus.^{3a-j} In the case which follows, probably the one hundred twenty-fourth to be reported, an aneurysm of the pulmonary artery apparently developed while the patient was under observation.

CASE REPORT

The patient, a 12-year-old Filipino girl, had been under observation at the Palama Settlement Medical Clinic since the age of 6 years because of cardiac enlargement and a family history of tuberculosis. During this six-year period, various descriptions of her cardiac abnormalities were recorded. In 1937 it was stated: "Heart enlarged outside nipple line one inch. No edema. Harsh systolic murmur loudest in the pulmonary area." A roentgenogram of the chest at that time was said to have shown cardiac enlargement and no evidence of tuberculosis. In 1939 a systolic thrill was present in the second left intercostal space. There were repeated statements regarding her poorly nourished appearance. Cyanosis and clubbed fingers were not observed at any time.

On March 11, 1942, the patient came to the Palama Clinic complaining of a painful right foot. There was no history of injury. A small reddish spot was present on the sole of her right foot. It was noted that there was no history of rheumatic fever and that a congenital cardiac lesion was to be considered. The record stated: "The lesion on the foot may be embolic." A roentgenogram of the chest showed cardiac enlargement (Fig. 1). She returned to the Clinic three weeks later, complaining of dyspnea after mild exertion. The foot lesion had disappeared. Her temperature was 98.8° F., and the physical signs were as noted above. She was again brought to the Clinic in May, after having been kept at home in bed for three weeks because of fever. Her temperature was 102.2° F., and her pulse rate was 116. Sulfathiazole was ordered in a dose of 3 Gm. daily for six days, but her response to this therapy is unknown because she did not return to the Clinic as directed.

The patient was first examined by one of us on July 3, 1942, after

From the Palama Settlement Medical Department and the Kapiolani Children's Hospital.

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she had coughed up a small amount of bright red blood. Examination revealed an emaciated, underdeveloped, dyspneic, 12-year-old girl. There was no cyanosis or clubbing of the fingers. The skin was pale, and coarse hyperkeratoses were present over the back and chest. Arterial pulsations were prominent in the neck. Marked bronchial breathing was present at the left base posteriorly. The heart was enlarged to the left. Gallop rhythm was present at the apex, and a loud systolic murmur was noticed in the second left intercostal space, with a thrill in systole. No diastolic murmurs were found. The abdomen was moderately distended, and the spleen and other organs were not palpated. The extremities were thin and the reflexes were normal.

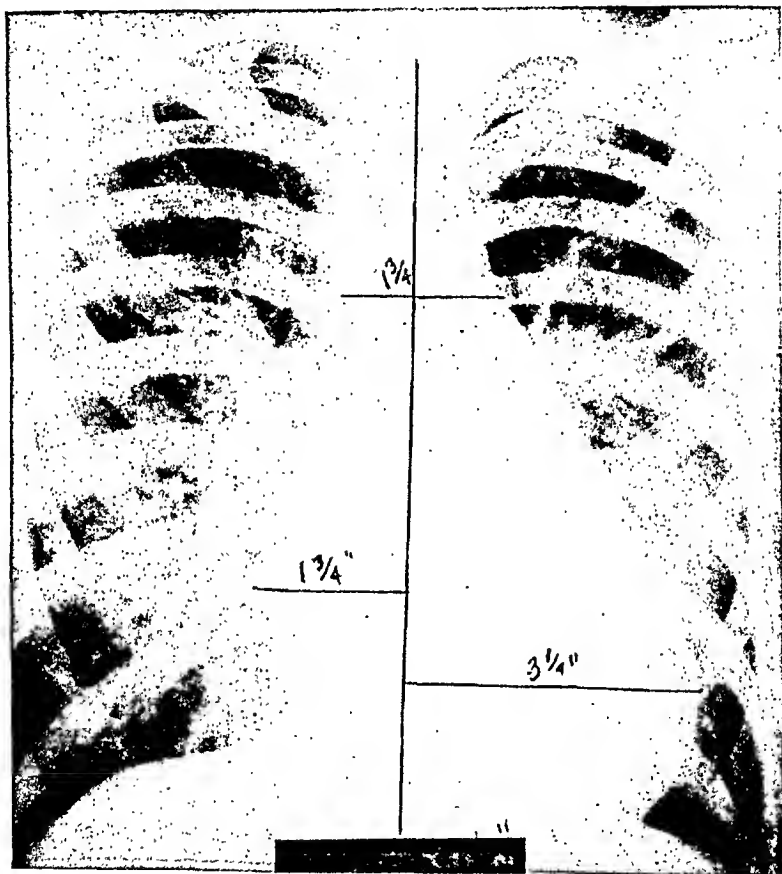


Fig. 1.—Roentgenogram taken March 11, 1942, four months before death.

Fluoroscopic examination of the chest showed marked prominence of the pulmonary conus area and vascular congestion. Otherwise, the lungs were normal. Both ventricles were greatly enlarged. Examination with barium showed no esophageal displacement.

Impression: Patency of the ductus arteriosus; malnutrition; subacute bacterial endocarditis?

She was referred to the Kapiolani Children's Hospital.

During the patient's twelve-day hospital stay her temperature varied from 99 to 101° F., and her pulse rate was consistently around 110. Dyspnea persisted, and she coughed up small amounts of blood occasionally. Her erythrocytes numbered 2,750,000 per cu. mm., and her

hemoglobin (Dare) was 50 per cent. Her leucocytes numbered 13,200 per cu. mm., and a differential count showed 92 per cent polymorphonuclear granular leucocytes and 7 per cent lymphocytes. Polychromatophilia and marked anisocytosis were observed. The urine contained no sugar, 1 plus albumin, and 4 to 5 leucocytes and occasional erythrocytes per high-power field. Three sputum examinations showed no acid-fast organisms. Two blood cultures were taken, and both were positive for *Streptococcus viridans*. She was given 7½ grains of sulfathiazole every four hours, and the usual supportive measures were taken.

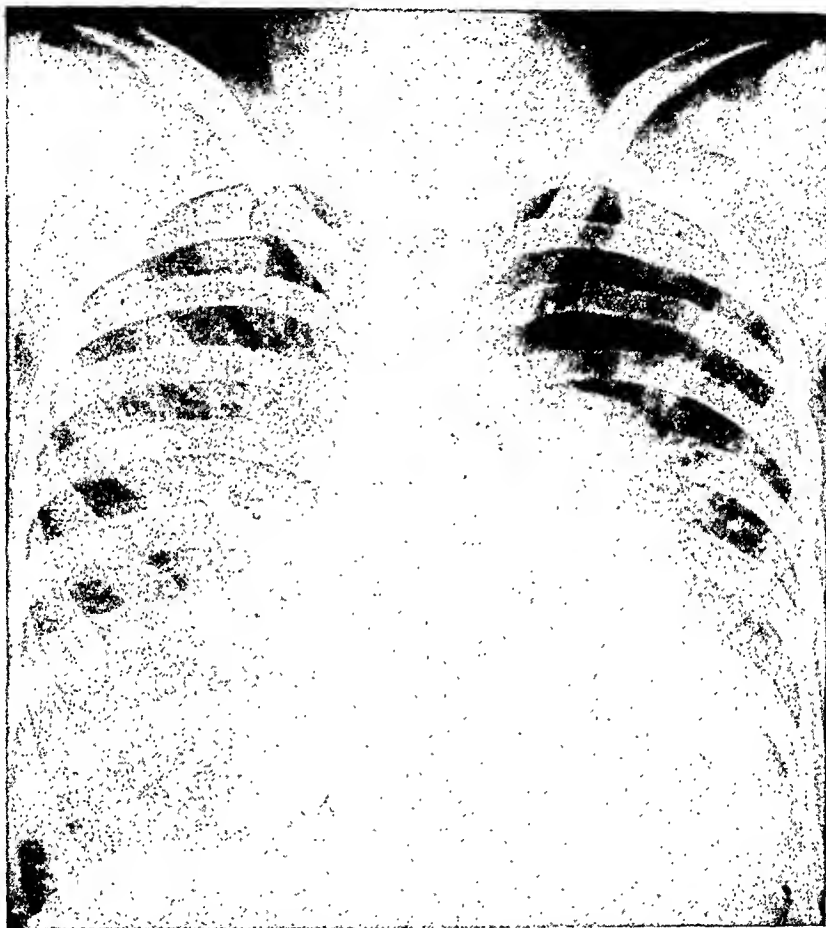


Fig. 2.—Roentgenogram taken July 13, 1912, two days before death. Note the changed appearance of the pulmonary conus area.

A roentgenogram of the chest revealed cardiac enlargement and marked prominence in the pulmonary conus area (Fig. 2). This was not present four months before (Fig. 1). On the tenth hospital day the patient complained of sharp pain in the right lower part of the chest, and coughed up small amounts of bright red blood. Two days later, upon awakening, she appeared to be quite weak and refused breakfast. A short time later she suddenly gasped for breath and died within a few minutes.

NECROPSY (SIGNIFICANT ABNORMALITIES)

The body was emaciated. No free fluid was present in the peritoneal cavity. The left pleural cavity was entirely obliterated by old ad-

hesions. The right lower pulmonary lobe was firmly attached to the chest wall by both old and recent adhesions. Both lungs were subcrepitant to noncrepitant throughout, and were deep purple in color. Both, upon sectioning, presented multiple infarcts of various sizes, several of which were broken down centrally. The intervening lung parenchyma was edematous and congested, although no areas of pneumonic consolidation were observed. Several calcified nodes were present near the left hilum, the largest of which measured $1\frac{1}{2}$ cm. in diameter.

The pericardial sac was filled with a large amount of blood clot and approximately 200 c.c. of serosanguineous fluid. An aneurysm about the size of a small lemon was found, arising from the anterior wall of the pulmonary artery just before its bifurcation. There was a recent linear tear, approximately 1 cm. in length, near the apex of the aneurysmal sac.

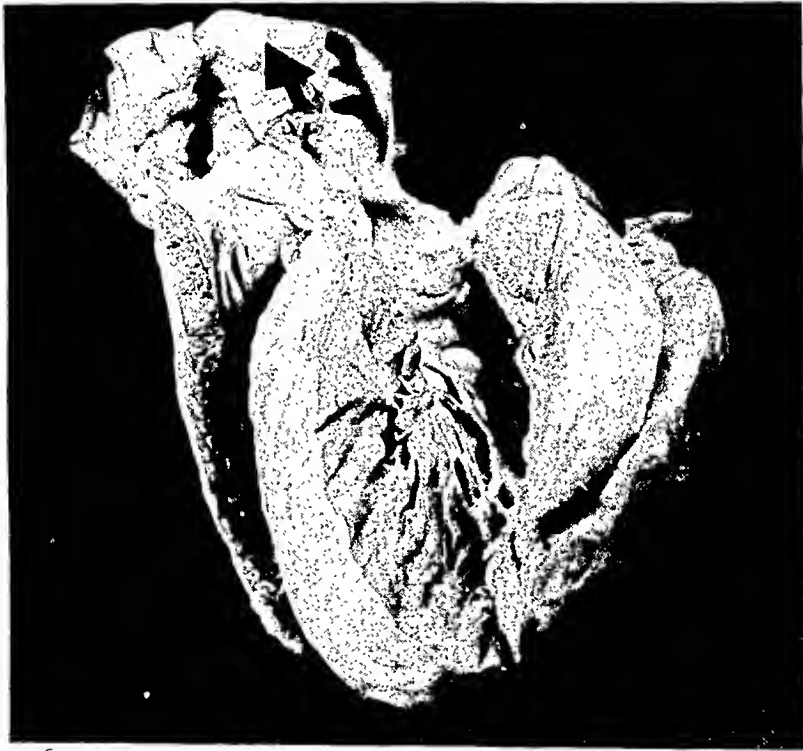


Fig. 3.—Arrow points to the patent ductus arteriosus. The aneurysm of the pulmonary artery is shown containing vegetations.

The heart was greatly enlarged (345 grams). The wall of the left ventricle measured 2 to $2\frac{1}{2}$ cm. in thickness, and the muscle was firm and pale in color. The mitral valve ring measured 9 cm., and a number of small, discrete, friable vegetations were present several millimeters above the free margin of the valve. There were similar vegetations on the endocardium of the left auricle more than 1 cm. above the free edge of the valve. The tricuspid, aortic, and pulmonary valves were normal in appearance.

The aneurysmal sac measured $3\frac{1}{2}$ cm. in diameter and $2\frac{1}{2}$ cm. at its base, which was located approximately 2 cm. above the pulmonary

valve ring. The aneurysmal wall was extremely thin, almost "paper-thin" in certain areas, and at no point measured more than a few millimeters in thickness. Numerous friable vegetations were attached to the base of the aneurysm and to the endocardial portion of its wall, and these extended for a short distance along the intima of the pulmonary artery. They were generally quite small; the largest measured slightly less than 1 cm. in diameter.

Opposite the opening of the aneurysmal sac there was a large, patent ductus arteriosus which communicated with the aorta just before the origin of the great vessels from the arch, (Fig. 3). It measured 1 cm. in diameter and possessed a smooth intima with no gross evidence of bacterial involvement.

The liver was moderately enlarged, and, upon sectioning, presented distinct vascular markings, i. e., the typical appearance of chronic passive congestion.

The spleen was enlarged and presented several firm, well-organized infarcts, the largest of which measured about 2 cm. in diameter.

The pancreas, adrenals, kidneys, pelvic organs, and gastrointestinal tract presented no gross abnormality.



Fig. 4.—Section of the aneurysm wall. A. Showing a widespread, diffuse inflammatory reaction ($\times 55$); B, Same, $\times 260$.

MICROSCOPIC STUDY

Examination of sections taken through the wall of the aneurysmal sac revealed widespread diffuse and focal inflammatory involvement (Fig. 4 A and B). The wall varied in thickness from place to place; generally, it was quite thin. The intima, for the most part, was entirely replaced by irregular patches of fibrin. Fibroblastic proliferation was prominent, and an interesting feature was the presence of miliary abscesses about the smaller blood vessels. Diffuse lymphocytic and plasma cell infiltration was present in most portions of the wall, and a generous sprinkling of polymorphonuclear granular leucocytes was observed. The cells mentioned above were concentrated about blood

vessels, many of which were newly formed, and consisted of a single layer of endothelium. Microscopic examination of the mitral valve showed moderate scarring, with hyalinization and loss of structure.

Patches of fibrosis were observed in sections taken through the left ventricle, and the individual muscle fibers were greatly hypertrophied. Many of the vessels were surrounded by cuffs of lymphocytes and mononuclear cells, but the histologic changes which are typically associated with rheumatic myocarditis were lacking.

Sections taken through the lungs revealed the changes associated with pulmonary infarcts of varying size and age; several of these exhibited tissue breakdown, and were characterized by the presence of acute cellular exudate in their central portions.

DISCUSSION

There is a strong possibility that the aneurysm of the pulmonary artery which ruptured and caused this patient's death was a fairly recent development in her illness. The roentgenogram which was taken four months prior to her death showed enlargement of the heart, but no prominence in the area of the pulmonary conus. In addition to the patent ductus, there may have been a small aneurysm of the pulmonary artery which could not be seen in an anteroposterior chest roentgenogram, but of that we have no proof. The prominence in the conus area, however, was most striking in the fluoroscopic examination, as well as in the roentgenogram taken after she entered the hospital.

About four months before death she began to have a fever, and suffered from a lesion which was most likely an embolism in the foot. Patients with uncomplicated patency of the ductus arteriosus commonly have an enlarged left ventricle,⁴ and, when they develop a superimposed infection on the site of the ductus, emboli may lodge either in the lung or in the peripheral circulation. The mitral valve, as well as the patent ductus, was the seat of vegetation in this patient. The former area may have given rise to the peripheral embolism. She also had numerous pulmonary infarcts which most probably came from the ductus vegetations.

The possibility that such vegetations may extend to the pulmonary arterial wall, and weaken it so that an aneurysm results, is mentioned by Scott.¹ Sections of the aneurysm wall in our case (Fig. 4) showed evidence of bacterial infection. The probability that the infection caused the pulmonary arterial wall to weaken, so that an aneurysm occurred, is thus given strong support. Boyd and McGavack,² in their review of the literature and discussion of the 111 cases in which the diagnosis was confirmed at autopsy, state:

"Congenital anomalies were present in 66 per cent of the cases and were deemed important etiologic factors in 43.2 per cent. Unequal division of the truncus arteriosus was evident in at least six, and open ductus arteriosus in twenty-four (23 per cent). Although pulmonary hypertension occurs in cases of patent ductus arteriosus and has been

regarded as causative of aneurysm, patency of this passage is not uncommon without aneurysm. Accordingly, it seems reasonable to assume that some additional lesion, such as superimposed infection or atheromatosis, may contribute to the production of the aneurysm in this group."

SUMMARY

Aneurysm of the pulmonary artery is rare.

A case is presented in which the aneurysm apparently developed while the patient was under observation.

There is evidence which strongly suggests that, in this case, the superimposed bacterial infection played a prominent role in producing the aneurysm.

We wish to express our thanks to Dr. J. Lam and Dr. W. B. Herter for permission to present the case, and to The Queen's Hospital Photographic Department for the photographs.

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STAPHYLOCOCCUS AUREUS SEPTICEMIA, WITH OSTEO-MYELITIS, PNEUMONIA, AND ACUTE PURULENT PERICARDITIS

CASE REPORT

CAPTAIN ROBERT R. IMPINK, MEDICAL CORPS, CAPTAIN ERIC DENHOFF, MEDICAL CORPS, AND MAJOR JOSEPH B. VANDERVEER, MEDICAL CORPS

THIS case history concerns a 4-year-old patient who was treated in an Army Evacuation Hospital on a semitropical island in the South Pacific area. The child was the victim of a fortuitous social condition, in that medical care on the part of local physicians was practically nonexistent because of the exigencies of the war. She, along with other ailing natives, was therefore forced to appeal to the American Army Medical Corps. The child suffered from a hemolytic *Staphylococcus aureus* septicemia, with secondary osteomyelitis of the right femur, acute purulent pericarditis, pneumonia, and pleurisy with effusion. Her apparently complete recovery is attributed to the combined use of chemotherapy and surgical treatment.

CASE REPORT

A 4-year-old Indigène girl, desperately ill, was brought to an Army Evacuation Hospital, May 23, 1942. Three days before admission she had fallen, and thereafter complained of pain in the right thigh. This pain increased in severity and made walking impossible. General malaise, chills, and fever developed. An officer of a field Army Medical Unit saw the child and noted fullness and tenderness in the right thigh. Suspecting a fracture, he brought the patient to the hospital for treatment.

The patient was the child of a white father, who was the son of an Australian settler, and a Melanesian mother.

Physical examination on admission revealed an extremely ill, malnourished native child, crying vociferously and striking and biting the attendants whenever the right thigh was manipulated. Dehydration was moderate. The temperature was 105° F., the pulse rate was 150, and the respiratory rate was 65. The lungs and heart were normal. An oval area, 3 by 6 cm., tender to palpation, was present on the anterolateral aspect of the right mid-thigh. No tenderness or swelling was noted in either the right hip or knee joint, although passive motion of both was restricted.

Roentgenograms of the pelvis and the right leg showed no abnormalities of the bones or joints. The erythrocyte count was 3,400,000, and the leucocyte count, 12,900; there were 67 per cent polymorphonuclear leucocytes, 6 per cent of which were juvenile. The urine contained a trace of albumin and 6 to 8 erythrocytes per high-power field.

From 52nd Evacuation Hospital, Colonel Ralph L. Cudlipp, Commanding; Lieutenant Colonel Henry P. Brown, Jr., Chief of Surgical Service.

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A diagnosis of acute hematogenous osteomyelitis of the right femur was made.

COURSE

Shortly after admission the child was given Ringer's solution parenterally, a transfusion of 65 c.c. of whole blood, and proctodysces of 2 per cent sodium bicarbonate solution. The right femur was immobilized in a plaster of Paris hip spica in order to eliminate pain and facilitate nursing care. The administration of sulfathiazole in a dose of $1\frac{1}{2}$ grains per pound of body weight per twenty-four hours was begun immediately. After twelve hours, sulfadiazine in the same dosage was substituted for the sulfathiazole. A blood culture which was taken shortly after admission was reported positive for *Staphylococcus aureus hemolyticus* in less than twenty-four hours. Multiple small transfusions were administered throughout the first week, as indicated on the chart (Fig. 2). During this period there was considerable improvement in her general condition, but lethargy, toxemia, and fever persisted.

On May 27, the fourth day after admission, the development of respiratory distress, a thready pulse of 176 per minute, a respiratory rate of 60 per minute, distended neck veins, and slight edema of the face and vulva suggested the presence of a complication. The cardiac dullness was found to be enlarged to percussion, the heart sounds were faint, and a pericardial friction rub was audible over the entire precordium. The administration of oxygen through a catheter in the nose was begun. On the following day there were physical signs of an area of consolidation in the upper lobe of the left lung. Examination of the right thigh through a window in the cast revealed more definite localization of the tenderness to the mid-shaft area, but no fluctuation. Another blood culture was positive. During the next few days there was slight improvement in the general condition, but edema of the face, extremities, and vulva became marked. Twitching and shaking of the head were traced to acute, bilateral otitis media. It was necessary to resort to gavage.

On May 31, eight days after admission, a roentgenogram of the chest showed considerable enlargement of the cardiac shadow (Fig. 1A). This was interpreted as probably due to cardiac dilatation, although pericardial effusion could not be ruled out. The pericardial friction rub persisted for several days, then gradually disappeared. A roentgenogram of the right femur showed periostitis of the mid-shaft area. Examination of the thigh on this date revealed an area of deep fluctuation. This was incised through a lateral approach, under local anesthesia. One hundred cubic centimeters of thick yellow pus were obtained. The abscess lay on the anterolateral aspect of the bone, and extended from the upper third of the shaft to a line just above the popliteal space. The bone had been denuded of periosteum in this area by the infectious process. After making a counterincision into the lower extremity of the cavity posteriorly, vaseline gauze packing was inserted and a plaster of Paris spica reapplied. On the following day the patient seemed much improved. *Staphylococcus aureus hemolyticus* was grown from a culture of pus taken from the abscess, and a blood culture taken just prior to operation showed the same organism. Because of this, bacteriophage, previously obtained through the courtesy of Dr. Ward MacNeal of the New York Postgraduate Hospital, was administered intravenously in increasing doses, beginning at 1:30 P.M. on June 1. There was no reaction

to this therapy, which was continued for one week. The maintenance dose of sulfadiazine was also continued during this period. The first blood culture to be reported negative was obtained on June 1, just before the bacteriophage therapy was initiated. With the subsidence of the blood stream infection the temperature became normal and the pulse and respiration rates diminished markedly. However, continuance of the septicemia was suggested by the appearance of multiple petechiae in the skin of the palms of the hands and beneath the nails of the fingers and toes. These lesions persisted for about one week. On June 6 the vaseline gauze was removed and reapplied more loosely into the abscess cavity of the thigh. A moderate amount of pus was present in the cavity as well as on the outer dressings. Because the edema had not regressed a plasma transfusion of 100 c.c. was given June 10. This was followed by diuresis. Sulfadiazine therapy was stopped on June 11 because the temperature was normal and an urticarial rash, which was suspected of being secondary to the drug, had developed.

In addition to edema of the face, extremities, and vulva, abdominal distention and hepatomegaly were noted on June 12. Examination of the heart revealed a marked increase in the area of cardiac dullness. The heart sounds were well heard with the patient in the semirecumbent position. Pulsus paradoxus was never noted. On June 14, aspiration of the pericardial sac yielded 110 c.c. of thin, cloudy, yellow fluid. Smears showed many pus cells, but no organisms. A culture of this material was negative. This tap and later ones were done in the fifth left intercostal space at approximately the anterior axillary line. The anasarca diminished at once, but a gradual rise in temperature followed. There were signs of pneumonitis in the left upper lobe. On June 17 the temperature reached 106° F., the pulse rate was 176, and the respiratory rate, 66 per minute. Sulfadiazine therapy was reinstituted. A roentgenogram of the chest showed marked enlargement of the cardiac shadow as a result of pericardial fluid, and also free fluid in the pleural cavity (Fig. 1B). On June 20, a thoracentesis was done, and 250 c.c. of thin, cloudy, yellow fluid were obtained. Culture of this fluid was negative. This was followed by improvement, as shown on the chart (Fig. 2). Sulfadiazine administration was discontinued June 27.

Because of recurrent generalized edema, a large tender liver, increasing cardiac dullness, and distant heart sounds the pericardial sac was aspirated a second time June 30, and 100 c.c. of cloudy fluid were obtained. Smears and culture of this fluid were negative. The child showed little change during the next ten days. A moderate degree of edema of the face and vulva and the large tender liver persisted. Two hundred twenty-five cubic centimeters of thin, cloudy, yellow fluid were removed July 12. Two days later a third pericardial tap yielded 175 c.c. of thin, purulent fluid (Fig. 1C). Smears of both these fluids showed many pus cells, but no organisms. The cultures were negative. After this last pericardial tap there was a rapid reaccumulation of fluid. The signs of elevated venous pressure did not subside after this aspiration, as they had previously. Consequently, during the week of July 19 three pericardial taps were performed, yielding 110 c.c., 50 c.c., and 60 c.c. of fluid, respectively. The fluid became thicker on each occasion, and could not be withdrawn completely. Despite the thick pus, smears showed no bacteria and the cultures were sterile. Because of lack of improvement in the general condition and the persistence of signs of cardiac failure, more adequate drainage of the pericardial space was essential.

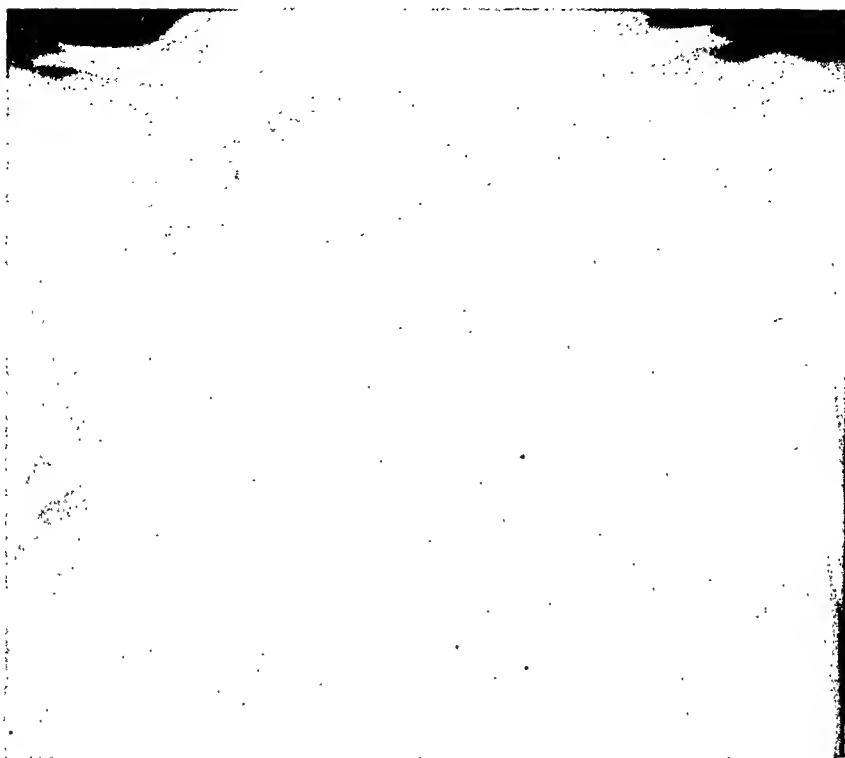


Fig. 1A.—May 31, 1942. The cardiac shadow is slightly enlarged.
The exposures in Figs. 1A, B, C, and D were made at a distance of seventy-two inches.

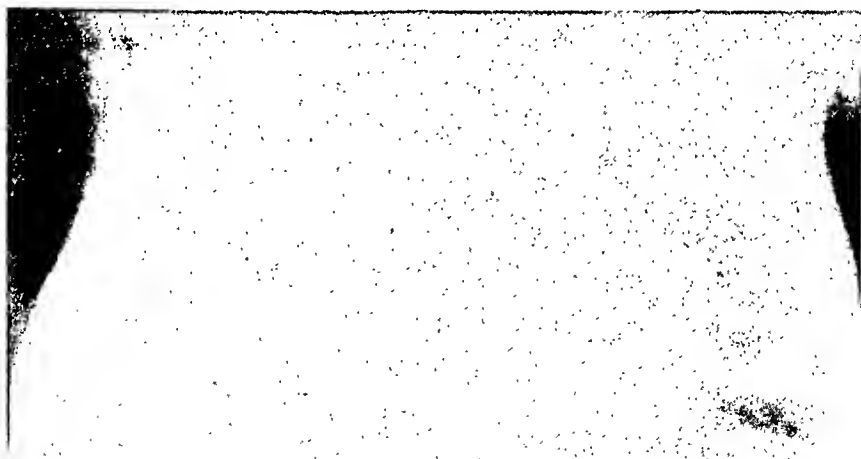


Fig. 1B.—June 17, 1942. Pericardial effusion, causing marked enlargement of the cardiac shadow.



Fig. 1C.—July 14, 1942. The thick wall of the pericardium is visible after aspiration of purulent fluid and injection of air.



Fig. 1D.—Aug. 31, 1942. Restoration of cardiac shadow nearly to normal.

A course of sulfadiazine therapy was begun July 27 in anticipation of a pericardiostomy. On July 31, open drainage of the pericardium was performed under local anesthesia through a space made by resecting the fifth and sixth costal cartilages. About 60 c.c. of thin, cloudy fluid and 60 c.c. of thick coagulated pus poured from the opening in the pericardium. A finger swept around the heart encountered no adhesions. The margins of the pericardial wound were sutured to the deep fascia to prevent spontaneous closure. A small plug of vaseline gauze was placed in the skin wound. Despite a stormy course during the first twenty-four hours after operation, the patient reacted well to the procedure. In the next few days the generalized edema diminished and the respiratory difficulty became less. It is interesting that a culture of the thick pus obtained at operation was reported positive for *Staphylococcus aureus hemolyticus*, although the fluid obtained by all the aspirations had been sterile. Drainage of a thin, purulent fluid was profuse for several days after the operation. Cultures of this fluid on August 3 and 5 were negative. The concentration of sulfadiazine in the blood and pericardial and pleural fluids during this period is recorded on the chart. The sulfadiazine was discontinued August 9, nine days after operation. Drainage subsided gradually and ceased August 10. Four days later the wound was closed by granulation tissue.

On August 5 the femoral wound was redressed for the third time. The cavity was about one-third its original size. A thin film of purulent exudate lined the cavity. A roentgenogram of the femur showed definite cortical bone regeneration, healing of the diaphyseal lesion, and no sequestrum formation. The abdominal portion of the plaster spica embarrassed respiration. No splint was reapplied. Routine stool examination shortly after admission to the hospital revealed the presence of the ova of *Ascaris lumbricoides*, *Taenia nana*, *Trichuris trichiura*, and *Necator americanus*. Two round worms were passed after attacks of severe colicky abdominal pains during the acute phase of the septicemia. Appropriate therapy was instituted during convalescence.

In the twelfth week of her illness the patient began to show signs of improvement. The temperature fell to normal, the pulse rate became stabilized at 120 per minute, which was lower than it had been since admission, and the respiratory rate varied between 28 and 32. Her appetite was voracious and she showed an increasing tendency to play and talk. The lesions in the right thigh filled with granulation tissue. On August 19, thirteen weeks after the incisions had been made, these lesions were healed. The femoral shaft, reinforced by periosteal osteogenesis, was not tender. The liver became painless to palpation, but its size decreased very slowly. When the patient was discharged, its edge could be palpated 7 cm. below the xiphoid process and 4 cm. below the costal margin in the right midclavicular line. There was no evidence of cardiac enlargement on physical examination, but a soft systolic murmur was audible over the entire precordium. The lungs were normal. Fig. 1D shows the condition of the chest on August 31, nine days before the child went home. At that time her strength was greatly improved, and at her own insistence she was permitted to stand on the affected leg and take a few steps.

The fever (see chart, Fig. 2) in her fifteenth week was caused by an upper respiratory tract infection. As soon as this complication had sub-

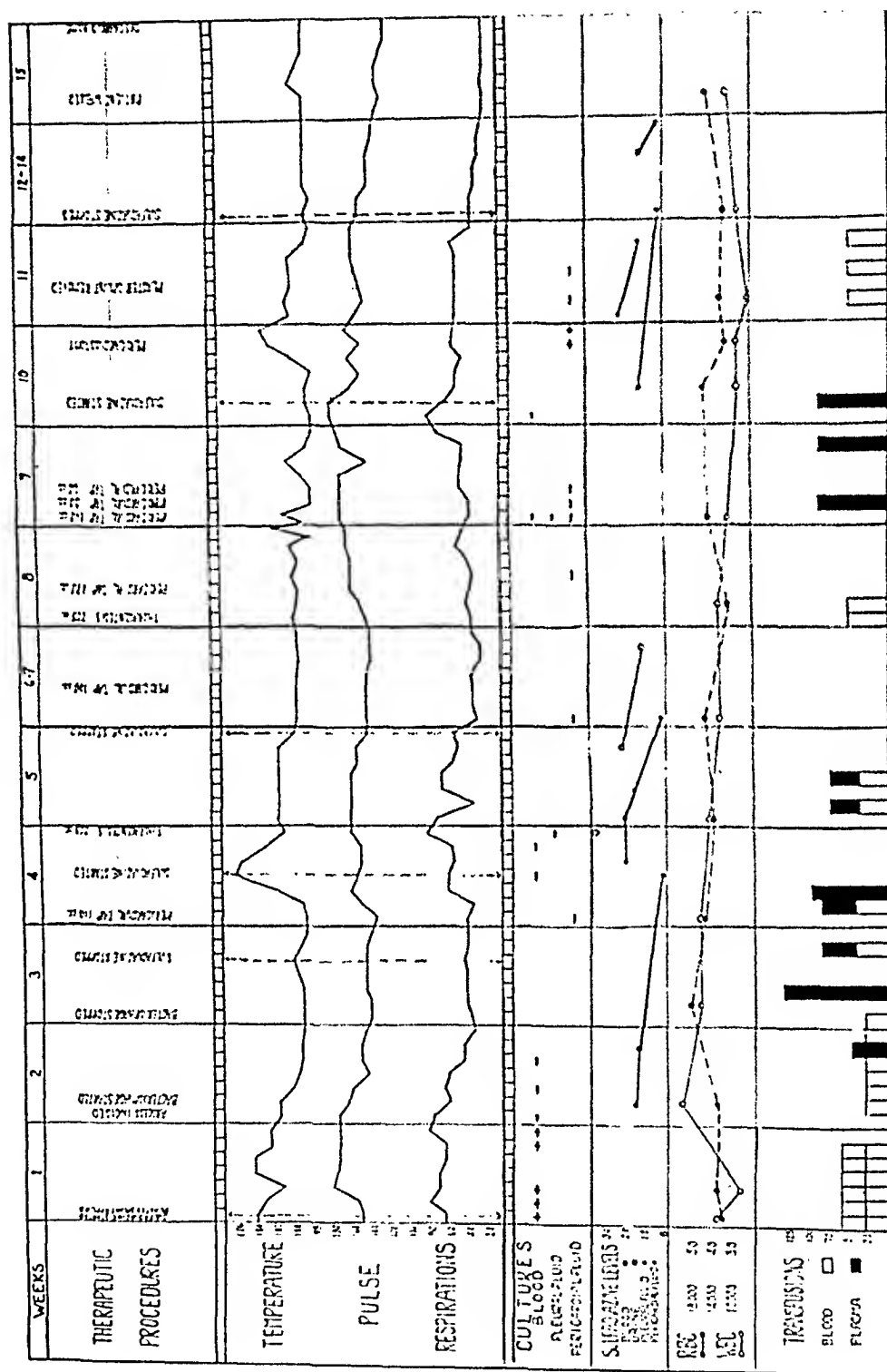


Fig. 2.—Composite chart of clinical and laboratory observations and therapeutic procedures.

sided she was sent home to continue her convalescence. The chest wound was covered by a thin crust, 4 mm. in diameter. We were dissuaded from a desire for more prolonged supervision of her recovery by the fear of recurrent infections to which she was subject in an Army Hospital in the field.

On October 8, one month after leaving the hospital, the child returned for a follow-up visit. Her general health had been good except for an attack of mumps. She had gained about ten pounds in weight and was able to play without embarrassment. Examination of the heart clinically and roentgenologically revealed no enlargement. The systolic murmur persisted over the entire preeordium. The liver was not tender, but had not diminished in size. No tenderness was elicited in the right thigh. Atrophy of the right thigh muscles was less pronounced, and the strength of these muscles had returned to about three-fourths of normal. There was full range of motion of both right hip and knee joints. A roentgenogram of the right femur revealed further deposition of new bone in the affected area and no evidence of sequestration.

DISCUSSION

This case was instructive because it demonstrated the efficacy of sulfadiazine in combatting septicemia with secondary osseous, pulmonary, and pericardial infections caused by *Staphylococcus aureus hemolyticus*. It provided us with working knowledge of a drug which promises to be extremely useful in our present situation.

The first blood culture from this patient contained 25 colonies of hemolytic *Staphylococcus aureus* per cubic centimeter at the end of twenty-four hours. A second culture, taken forty-eight hours later, contained 30 colonies per cubic centimeter. Eight days after the sulfadiazine had been started a blood culture was negative. Subsequent cultures remained sterile. The embolic phenomena in the skin, at first thought to be due to endocarditis, were probably a manifestation of the septicemia. In view of the fact that the blood culture taken just before the bacteriophage was begun was negative, and in view of the later excellent effect of the sulfadiazine alone, we believe that the bacteriophage played a negligible part in this case.

Pneumonia was encountered twice during the course of the illness. At neither time was the patient receiving sulfadiazine. This drug was started immediately and the pulmonary complication was controlled within twenty-four hours in both instances. After the original course of sulfadiazine had been discontinued for five days, the blood level of the drug had dropped to zero. The recurrence of pleural effusion, pneumonia, and pericarditis made it desirable to attain a high concentration of sulfadiazine in the blood as soon as possible. This was accomplished by administering sodium sulfadiazine in 5 per cent solution intravenously. Twenty-four hours after this, the blood level was 14.0 mg. per cent. Of particular interest was the concentration of 40 mg. per cent of sulfadiazine in the pleural fluid which was aspirated at the same time. Stained smears of this fluid revealed a mosaic of sulfadiazine

crystals. Effective blood levels of sulfadiazine were maintained at all times by an oral dose of $1\frac{1}{2}$ grains per pound of body weight per twenty-four hours. At no time during the administration of the sulfadiazine did we note any evidence of toxicity that might be attributable to chemotherapy except for an urticarial rash and the chronic anemia. The latter was more likely due to the infection than to the drug. There was no evidence of acquired tolerance or sensitivity to sulfadiazine during the second and third courses of administration.

The development of acute *Staphylococcus aureus hemolyticus* pericarditis presented a grave problem in view of the high mortality of this disease. We relied upon sulfadiazine as the most effective available therapeutic agent. When generalized edema and enlargement of the liver indicated cardiac tamponade, repeated aspirations were done. Each of the earlier aspirations resulted in improvement, but finally the fluid became too thick to be withdrawn through the available needles. Pericardiostomy was then performed, and recovery progressed steadily from that time.

The successful management of the osteomyelitis by simple immobilization of the leg and drainage of the soft tissue abscess was very gratifying. It confirmed our faith in this form of treatment. Although it is too early to be certain that further local or metastatic bone and joint infections will not arise, each week diminishes the probability of such an occurrence. The advisability of permitting weight-bearing as early as we did in this case is debatable. Thus far, no ill effects have been noted.

During the early stages of treatment the multiple, small, whole-blood transfusions seemed invaluable. Later, blood transfusions were given whenever the erythrocyte count fell below 3,600,000 per cubic centimeter.

When generalized edema appeared, frequent plasma transfusions were utilized. Plasma protein estimations were not available, but we felt that the edema was due, at least in part, to hypoproteinemia. The multiple foci of infection and low protein and low vitamin intake, with liver damage from passive congestion, were sufficient to cause hypoproteinemia. It is unlikely that hypoproteinemia was a primary factor in the edema, for the latter was not dispelled by large infusions of plasma until the pericardium had been drained adequately.

The prognosis in this case is guarded, but we are optimistic. We feel that it is unlikely that any permanent embarrassment of cardiac function will result. The possibility of the development of a constrictive pericarditis from contraction of the pericardial scar cannot be predicted nor excluded at this time.

SUMMARY

Sulfadiazine and surgical treatment were largely responsible for the recovery of a child with *Staphylococcus aureus hemolyticus* septicemia, complicated by osteomyelitis, pneumonia, and purulent pericarditis. The treatment was carried out in an Army Evacuation Hospital in the field.

We are indebted to Sergeant Richard Nobbe and Corporal Bernard Piper, of the United States Army Medical Corps, for valuable assistance in the laboratory studies and for their donation of blood for transfusions.

ADDENDUM

The child has been examined at regular intervals since leaving the hospital. There has been a gradual return of strength and weight, so that, eight months after discharge, she is essentially normal. At the time of her last examination there was no evidence of cardiac enlargement, and the murmur had disappeared. Her response to exercise was normal, and there was no evidence of venous engorgement. The hepatomegaly had entirely disappeared, and the spleen was not palpable. There was no evidence of recurrence of the osteomyelitis at the original site or elsewhere, and the right leg was being used in a normal manner. A roentgenogram of the chest showed that the cardiac shadow was within normal limits and that the lungs were normal.

Abstracts and Reviews

Selected Abstracts

Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C.: Effects of Exercise on the Coronary Blood Flow, Heart Rate and Blood Pressure of Trained Dogs With Denervated and Partially Denervated Hearts. *Am. J. Physiol.* 138: 687, 1943.

Observations have been made on the coronary blood flow, heart rate, and blood pressure of trained dogs after the following procedures: bilateral sympathetic ganglionectomy, from the eighth costal interspace anteriorly, including the stellate ganglion; double cervical vagotomy; right vagotomy followed by left vagotomy; cardiac sympathectomy and right cervical vagotomy, followed by left cervical vagotomy. Blood flow in the circumflex branch of the left coronary artery was observed by use of the thermostromuhr. Blood pressure was recorded optically from a cannulated femoral or carotid artery. The heart rate was observed electrocardiographically.

The effects of exercise on animals that had sympathectomized hearts were not essentially different from results obtained in animals that had innervated hearts. In both series exercise produced increased coronary blood flow, pulse rate, and blood pressure. The observations were made 24 to 124 days after sympathetic ganglionectomy. The effects of exercise were very similar in animals on which complete cardiac denervation had been performed and those lacking only the vagi. Loss of the vagi affected cardiac acceleration profoundly. Vagotomized hearts increased only about 10 to 20 beats each minute with increments in the rate of work. This was true whether or not the sympathetic nerves were present. In the absence of marked acceleration and elevation of blood pressure, the coronary blood flow was not affected by exercise. In animals that had vagotomized or totally denervated hearts, the coronary blood flow appeared to be influenced chiefly by the blood pressure.

AUTHORS.

Taylor, H. L., Henschel, A. F., and Keys, A.: Cardiovascular Adjustments of Man in Rest and Work During Exposure to Dry Heat. *Am. J. Physiol.* 139: 583, 1943.

Seven thousand observations on pulse, blood pressure, rectal temperature, and rate of sweating in work and rest are reported on forty-three subjects (202 subject days) on a constant salt diet before and during exposure to dry heat for two to eight days. Additional observations were made on twenty-three other subjects for 147 subject days. Observations of pulse and blood pressure before and after elevation on a tilt table were made morning and evening. Modified Crampton scores of cardiovascular fitness were calculated from these figures.

Marked deviations from control values in cool conditions were observed in work pulse rates, rectal temperatures, and Crampton scores during the first days in heat.

Ten cases of heat exhaustion occurred; four of these were clear-cut examples showing collapse with hypotension, tachycardia, vertigo, and vomiting. Rest without removal from the hot environment sufficed to restore the ability to perform work in these men.

A rapid improvement in work pulse rate, rectal temperature, and Crampton

score took place and was complete in four to five days. No significant change took place in these variables from the fifth to eighth days.

The primary adjustment involved in acclimatization to heat is an improvement in cardiovascular efficiency. A decrease in the accumulation of heat, as measured by rectal temperature during work, is probably secondary to cardiovascular improvement.

The average daily sweat loss is not affected by acclimatization. The rate of sweating during work tends to increase as acclimatization proceeds, but a large part (one-half) of this change occurs after the more important adjustments, as indicated by the rectal temperature and pulse rate during work, have taken place.

The failure of the work pulse rate to show improvement over the value of the first day is a sign of impending heat exhaustion; similarly, poor cardiovascular postural adjustment in the evening is a danger sign.

None of the variables studied in the cold (control) are useful in the prediction of the ability to acclimatize in subsequent exposure in heat.

AUTHORS.

Barrow, W. H., and Ouer, R. A.: *Electrocardiographic Changes in Exercise: Their Relation to Age and Other Factors.* Arch. Int. Med. 71: 547, 1943.

With a series of 100 normal men, a study was made of the electrocardiographic changes produced by vigorous participation in such active sports as handball and badminton. Tracings were taken immediately before and immediately after exercise.

There were no significant changes in the auriculoventricular or the intraventricular conduction time. Inversion of the P wave in Lead CF₁, after exercise, occurred in about half the group. Changes in the T wave were limited to changes in voltage. These were common, but no frank inversion of the T wave or distortion of the S-T segment was found. A change in the size of the QRS complex was most common, being found in four-fifths of the men in the series.

Half of the men studied were under 40 years of age, with an average age of 31 years, while the other half were over 40 years, with an average age of 49 years. There were no significant electrocardiographic differences between the two age groups, although the incidence of change, when it did occur, was greater in the younger group.

Concurrently, a determination of the Schneider index was made for each subject. There was no marked difference in the average rating of the two age groups. There was no demonstrable correlation between the Schneider index rating and the electrocardiographic changes noted with exercise.

Three-fifths of the men studied were smokers. The smokers had a Schneider index slightly lower than the nonsmokers, and changes in the P wave in Lead CF₁, and in the T wave were more frequent in this group. In the course of the investigation there were found a few distortions of T, S-T, and QRS, which disappeared with vigorous and prolonged exercise, and which may therefore be considered as occasional variants of the normal electrocardiogram.

AUTHORS.

Weinberg, T., and Himelfarb, A. J.: *Endocardial Fibroelastosis (So-Called Fetal Endocarditis). A Report of Two Cases Occurring in Siblings.* Bull. Johns Hopkins Hosp. 72: 299, 1943.

Two cases of fibroelastosis of the endocardium occurring in siblings are presented. This, together with the lack of history of any type of infection in the mother during both periods of pregnancy, militates strongly against the concept of fetal endocarditis as implying an intrauterine infection and just as strongly

supports the suspicion of an inherent developmental defect. Further support for the latter theory is seen in the lack of inflammatory stigmata in either the endocardium or myocardium.

An explanation is offered for the ultimate left heart failure in these cases.

AUTHORS.

Crawford, J. H.: Aneurysm of the Heart. *Arch. Int. Med.* 71: 502, 1943.

There are no symptoms characteristic of aneurysm of the heart. It may be asymptomatic, but, as a rule, some symptoms due to congestive heart failure are present. Sometimes angina pectoris is the only complaint.

The signs which are most frequently present and appear to be most important in the diagnosis of aneurysm of the heart are: a history or electrocardiographic proof of coronary occlusion; the presence of an abnormal precordial pulsation distinctly separated from the apex pulsation, particularly when it is situated above the fifth rib; on roentgen examination, a localized bulge which cannot be separated from the heart shadow in any view in which it can be seen, or an angulation of the left border of the heart; systolic expansion in the region of the abnormality as seen on fluoroscopic or roentgenokymographic examination, which is practically conclusive evidence, and small contractions or none in this area, which are strongly suggestive; and localized pericardial adhesions or calcification of the aneurysmal wall or its contents.

The following conditions simulate aneurysm of the heart most closely and must be carefully differentiated from it: tumor of the heart; aneurysm of a sinus of Valsalva; aneurysm of a coronary artery; calcification of the pericardium; diverticulum of the pericardium; loculated pericardial effusion; and cyst of the pericardium.

AUTHOR.

Miller, W. S., and Woods, W. W.: Fatal Coronary Thrombosis in a Man Aged Twenty-Two. *Brit. Heart J.* 5: 101, 1943.

A case of sudden unexpected death from coronary thrombosis and ischemic fibrosis of the myocardium is described in a man 22 years of age. Thrombosis had occurred in the anterior descending branch so long before death that the thrombus was completely organized and contained vessels with musculo-elastic walls. There was a more recent incompletely organized thrombus in the circumflex branch. The examination revealed neither a thrombus that had formed immediately before death nor a recent myocardial infarct. The only disease found in the coronary arteries predisposing to thrombosis was atheroma. There was no history of any illness before the attack, which started about one hour before death.

The reported cases of coronary thrombosis in young adults are reviewed. The condition in young adults is very similar to the typical case in later life except that raised blood pressure has rarely been noted. The pathologic lesion found in the cases that have come to necropsy is atheroma (atherosclerosis) of the coronary arteries, the anterior descending branch of the left coronary being most frequently the site of the thrombosis.

AUTHORS.

Smith, J. J., and Furth, J.: Fibrosis of the Endocardium and the Myocardium With Mural Thrombosis: Notes on Its Relation to Isolated (Fiedler's) Myocarditis and to Beriberi Heart. *Arch. Int. Med.* 71: 602, 1943.

Three cases of heart failure in young adults which is not attributable to arteriosclerosis, hypertension, or valvular heart disease are reported.

The most striking pathologic features are endocardial and myocardial fibrosis, and cardiac hypertrophy and dilatation in the absence of vascular or valvular change. The endocardial fibrosis and cardiac failure predispose to mural thrombosis with emboli. These changes resemble those previously described in the literature under the term isolated myocarditis.

The question is raised whether these changes could have been associated with deficient diet and could represent a variant of beriberi heart.

AUTHORS.

Pasqualini, R. Q., and Donnes, A. V.: Frequency of Acute Polyarticular Rheumatism in Argentina. *Rev. argent. de cardiol.* 9: 367, 1943.

The frequency of rheumatic fever among three hundred thousand 20-year-old men from the Argentine army over a period of eight years has been analyzed. In this period there were 1,288 cases of rheumatic fever, which gives a global proportion of 4.3 per cent.

The frequency was greater in the Atlantic littoral, in the Patagonian region, and in the east-central zone; it was medium in the river littoral, and smallest in the northern region. The maximum frequency occurred during August and September, except in the Patagonian region, where it occurred in June.

The frequency observed should be considered very high if compared with data obtained in other parts of the world.

AUTHORS.

Jones, E., and Bedford, D. E.: Syphilitic Angina Pectoris. *Brit. Heart J.* 5: 107, 1943.

A series of 103 syphilitic patients subject to paroxysmal pain in the chest has been investigated with special regard to the clinical characteristics of the pain and its pathogenesis.

The age of onset of pain was evenly distributed over the fifth, sixth, and seventh decades, its maximal incidence being actually between 40 and 50 years. There were 80 men and 23 women, giving a sex ratio of 3.5 to 1. A history of syphilitic infection was obtained in 31 cases; the average period between infection and the onset of pain was 24 years. A positive Wassermann reaction was recorded at some stage in 96 cases.

The main clinical findings were aortic incompetence in 67 cases; dilatation of the aorta in 59; cardiac enlargement, often slight, in 83; and essential hypertension in 26. Abnormal cardiograms were recorded in 57 of 94 cases examined.

Seventy-six patients were subject to angina of effort and 64 had pain apart from effort. Nocturnal attacks were common and were usually independent of paroxysmal dyspnea. They tended to be prolonged but were relieved by nitrites. Paroxysmal anginal attacks occurred in 13, a syphilitic status anginosus in 9, and symptoms of coronary thrombosis, not attributed to syphilis, in 10 cases.

Post-mortem findings in 12 cases are given, and other pathologic data are considered. The essential lesions of syphilitic angina are aortitis and aortic incompetence, usually combined with stenosis or occlusion of the coronary ostia. Atheromatous and thrombotic coronary occlusion may be coincident with syphilitic aortitis. Pathologic evidence that uncomplicated aortitis causes anginal pain is lacking.

The thesis of an atypical or pseudo-anginal syndrome due to aortitis is examined and rejected. Paroxysmal pain in syphilitic cases conforms to recognized clinical varieties of angina pectoris such as are encountered in nonsyphilitic coronary and aortic disease. Aortic incompetence and obstruction of the coronary ostia, which affect the blood supply to the whole heart, and cause widespread rather than focal

cardiac ischemia, predispose to spontaneous and prolonged pain. The horizontal posture appears to be an important exciting cause of these nocturnal attacks. In paradympneic pain, the effect of posture may be largely mechanical, but in other cases a reflex nervous mechanism may be operative. Consideration of certain cases also suggests that a relationship may exist between pressure pain from a dilated aorta and recumbency.

The clinical course, prognosis, and treatment are briefly described.

AUTHORS.

McGavack, T. H.: Angina-Like Pain: A Manifestation of the Male Climacterium. J. Clin. Endocrin. 3: 71, 1943.

Severe angina-like pain was observed in eight patients, which did not respond to treatment with vasodilator drugs and sedatives, but was promptly relieved by the administration of testosterone. When looked for, other evidence of changing testicular function was present, such as impotence, easy tiring, myalgic and arthralgic pains, vague digestive complaints, mild genitourinary symptoms, insomnia, and vasomotor disturbances. As a group, these patients represent a syndrome in which some cardiovascular disturbance, notably precordial pain, is the predominant expression of the male climacterium. Their failure to respond to the usual vasodilator drugs distinguishes them from other forms of angina pectoris which may or may not be relieved by sex hormone therapy. The influence of testicular hormones on cardiac activity is briefly discussed.

AUTHOR.

Duncan, G. W., Hyman, C., and Chamber, E. L.: Determination of Blood Pressure in Rats by Direct Observation of Blood Vessels. J. Lab. & Clin. Med. 28: 886, 1943.

The arterial blood pressure of rats may be rapidly and easily determined by microscopic observation of the flow of blood in the small arterial vessels of the interdigital web. Values obtained by this method agree with pressures determined by aortic cannulation and with those reported in the literature.

AUTHORS.

Cromartie, W. J.: Arteritis in Rats With Experimental Renal Hypertension. Am. J. M. Sc. 206: 66, 1943.

A form of arteritis similar to that described as occurring spontaneously in rats over 500 days of age has been found to occur in a high percentage of rats 400 days of age, which had developed either arterial hypertension and a suppurative infection of one or both kidneys, or arterial hypertension unassociated with renal infection, following the application of a layer of cotton cloth to the surface of one or both kidneys.

The pathologic anatomy of this disease is described, and the similarity of these lesions to the lesions of periarteritis nodosa of man is pointed out.

Other arterial changes which do not seem to be related to the inflammatory arterial disease are described and a possible factor in their pathogenesis is discussed.

AUTHOR.

Page, I. H., Taylor, R. D., and Kohlstaedt, K. G.: A Case of Extreme Hypotension Following Acute Arsenic Poisoning With Adequate Blood Supply to the Tissues. Am. J. M. Sc. 205: 730, 1943.

A paretic was studied who took 15 Gm. of arsenic trioxide with suicidal intent. He was able to walk and cooperate despite the fact that mean intra-arterial blood

pressure was only 30 mm. Hg. The other striking feature was that tissue perfusion seemed excellent; the only function appearing to suffer being the ability of the kidneys to secrete urine.

The patient was able to maintain adequate perfusion of the tissue by doubling the output of the heart and greatly reducing peripheral resistance. The renal vasopressor system did not respond to the hypotensive stimulus possibly because pulse pressure was not reduced.

The patient seemed to have few ill effects from this episode except that, associated with it, reactivations of general paresis, from which he had previously suffered, occurred, leading to his death.

This clinical experiment suggests that reduction in arterial pressure need not lead to serious consequences if the perfusion of the tissues remains adequate. In this respect the clinical picture was the reverse of shock in which both arterial pressure and tissue perfusion are severely reduced. The importance of obtaining better tissue perfusion in shock rather than elevating arterial pressure, the converse of the hemodynamic state in this patient, is suggested by these observations.

AUTHORS

Holt, J. P.: The Effect of Positive and Negative Intra-Thoracic Pressure on Peripheral Venous Pressure in Man. *Am. J. Physiol.* 139: 208, 1943.

Venous pressure was determined in the antecubital vein by a modification of the direct method of Moritz and Tabora in eight normal subjects who breathed from a chamber in which the pressure was varied from 14 cm. of water above to 14 cm. below atmospheric. In the supine subject, with the arm held well below heart level, the peripheral venous pressure decreased when air under negative pressure was breathed, and increased when air under positive pressure was breathed. When the arm was held well above heart level, in the supine subject, the peripheral venous pressure remained constant when intrathoracic pressure was decreased. In the sitting position the peripheral venous pressure remained constant when the intrathoracic pressure was decreased.

In normal man, in the supine position with the arm well below heart level and abducted to 45 degrees, peripheral venous pressure is a function of right auricular pressure.

AUTHOR.

Lisa, J. R., Eckstein, D., and Solomon, C.: Relationship Between Arteriosclerosis of the Renal Artery and Hypertension: Analysis of 100 Necropsies. *Am. J. M. Sc.* 205: 701, 1943.

The caliber of the renal arteries was studied in 100 consecutive cases in which blood pressure readings were obtained. Hypertension was present in 56, normal pressures were found in 44. Marked variations were found in the caliber of non-sclerotic vessels when measured in the fresh state and in the fixed stained preparation; therefore, only the figures obtained in the fresh state were used for analysis. The differences of caliber between sclerotic vessels of the hypertensive and nonhypertensive cases were insignificant. Only two instances were found simulating the Goldblatt kidney. The degree of cholesterol deposit bore no relationship to the caliber. The degree and extent of arteriolar sclerosis estimated from the histologic examination of the kidneys proved a better index of the blood pressure readings than the caliber of the main renal arteries. The data lend more support to the theory advanced by Page than that of Goldblatt for the development of hypertension.

AUTHORS.

Megibow, R. S., Katz, L. N., and Feinstein, M.: Kinetics of Respiration in Experimental Pulmonary Embolism. *Arch. Int. Med.* 71: 536, 1943.

Respiration following embolism of major and moderately sized pulmonary arteries is characterized by tachypnea, dyspnea, and hyperpnea; that following embolism of pulmonary arterioles and capillaries is characterized primarily by tachypnea.

These changes are not dependent on anoxemia, since the onset of rapid breathing is not infrequently associated with an increase in the oxygen content and per cent oxygen saturation of the arterial blood.

Alterations in carbon dioxide content and in pH of the blood similarly play insignificant roles, since hypercapnia is inconstant and when occurring is transitory, while respiratory variations occur prior to any tendency to acidemia.

Actual decreases in volume and variations in elasticity in the lungs, such as follow congestion, edema, and atelectasis, while later adding definitive increases to the already accelerated respiration, are by themselves not fundamentally implicated.

Evidence is presented to show that the respiratory changes are not mediated centrally by circulatory slowing through the respiratory center.

The fact that bilateral vagotomy constantly converts rapid postembolic breathing into slow vagal breathing is utilized as further evidence that the production of rapid breathing is peripheral rather than central.

The intimate relation of vascular obstruction to rapid breathing is indicated, and the fundamental mechanism with all varieties of pulmonary embolism is shown to be stimulation by distention of afferent nerve endings scattered throughout the pulmonary arterial bed, right side of the heart, and superior vena cava.

Through rapid increases in elasticity of the lungs, secondary reflexes are initiated altering the primary respiratory response, and these account for the absence of dyspnea and hyperpnea in miliary embolism.

A brief consideration of the therapeutics of postembolic respiration shows that of the drugs studied, only papaverine exerts any beneficial action.

There is a possibility that reflexes of similar origin may be responsible for dyspnea in congestive heart failure and acute failure of the left side of the heart.

AUTHORS.

Menes, H. J., and Quesada, J. J.: Normal Cardiovascular Roentgen Silhouette Studied by Means of Roentgenograms of the Chests of Cadavers After Opaque Solutions Had Been Injected Into the Large Vessels and Chambers of the Heart. *Arch. Int. Med.* 70: 666, 1943.

The right side of the cardiac silhouette is formed from the cranial end downward by a short, nearly vertical segment corresponding to the innominate vessels, by the so-called right superior arch, which normally corresponds to the superior vena cava, placed normally to the right of the ascending aorta, and by the inferior right arch, corresponding to the right atrium. The very short straight segment sometimes visible in the lower part of this silhouette is formed by the inferior vena cava. The suprahepatic veins were totally subdiaphragmatic in the cadavers studied.

The left side of the cardiac silhouette is formed from the cranial end downward by a straight segment corresponding to the left carotid and left subclavian arteries, by the middle arch, corresponding on its upper portion to the left division of the pulmonary artery, on its middle portion to the pulmonary artery, and on its lower portion to the left atrium, and by the inferior left arch, corresponding to the left ventricle.

In the roentgenograms the lower and outward pole of the shadow of the heart, usually called the apex, corresponds entirely to the left ventricle.

The shadows normally obtained at the sites of the pulmonary hili correspond to the branching of the right and the left division of the pulmonary artery. They are mainly vascular and even arterial in nature.

The silhouette of the heart and vessels in a right anterior oblique position is formed on the spinal side by the superior vena cava on its upper portion and by the right atrium on its lower portion. This same silhouette is formed on the ventral side from the cranial end downward by the ascending aorta (the innominate vessels and the left carotid and subclavian arteries being nearly transparent to roentgen rays), the pulmonary artery and its left division, and the left ventricle.

The silhouette of the heart and large vessels in roentgenograms taken in a left anterior oblique position is formed on the ventral side by the superior vena cava on the upper portion, by the ascending aorta on the middle portion, and by the right ventricle on the lower portion. On the spinal side it is formed on the upper part by the aorta, on the middle portion by the pulmonary artery, and on the lower portion by the left atrium.

Normally, only the ascending portion of the aorta is visible on a roentgenogram taken in a left anterior oblique position, the transverse portion being superimposed on the tracheal clearness and the descending portion on the shadow of the vertebrae.

AUTHORS.

Shumacker, H. G., Jr.: Sympathectomy in the Treatment of Peripheral Vascular Disease. *Surgery* 13: 1, 1943.

The value of sympathectomy in the treatment of disorders of the peripheral circulation has been discussed. The study of patients in an attempt to evaluate the possible benefit of sympathectomy is outlined, the operative technique of dorsal and lumbar sympathectomy is described, and the results in sympathetic denervation of eighty-three extremities is presented.

AUTHOR.

Hedley, O. F.: The Fraudulent Use of Digitalis to Simulate Heart Disease. *Ann. Int. Med.* 18: 151, 1943.

Altogether, 81 persons were actively involved. Of these, 6 were convicted after trial, 38 pleaded guilty, 16 were indicted but pleaded not guilty, 20 confessed but were not indicted, and 2 were arrested but not indicted. In addition, there were 155 others against whom there was evidence of guilt but who have not been arrested, or indicted, or have not confessed.

Two physicians were convicted after trial, 7 pleaded guilty and were sentenced, 3 were indicted but pleaded not guilty, 10 confessed but were not indicted, while among 11 others there was evidence of guilt at hand but they were not arrested, indicted, or convicted. Many other physicians unwittingly certified claimants as having heart disease and were occasioned embarrassment and loss of time.

Life insurance policies amounting to more than ten million dollars in more than forty different life insurance companies were involved. Actual payments and cash settlements amounting to several hundred thousand dollars were made. The most important feature of this conspiracy was that as a result of this and other fraudulent practices, the cost of disability insurance has greatly increased, and most insurance companies have ceased issuing this form of insurance. This vitally affects many honest citizens who might otherwise receive this protection.

AUTHOR.

Frankel, D. B., and Wakerlin, G. E.: Excretion of the Urinary Antidiuretic Principle in Renal Hypertensive Dogs. *Am. J. Physiol.* 138: 465, 1943.

The excretion of the urinary antidiuretic principle in dogs during normal hydration and during dehydration was not changed by the production of experimental renal (Goldblatt) hypertension.

These results do not support, but do not rule out, the possibility of altered posterior pituitary function in experimental renal hypertension in the dog.

AUTHORS.

Little, J. M., and Wells, H. S.: Capillary Permeability to Intravenously Administered Gelatine. *Am. J. Physiol.* 138: 495, 1943.

It has been shown that intestinal capillaries injured sufficiently to permit the partial or complete passage of serum proteins through their walls allow the passage of only 35 to 60 per cent of plasma gelatin. This is thought to be due either to a slower rate of escape for gelatin than for serum proteins or to the presence of gelatin particles to which the injured capillary is completely impermeable.

AUTHORS.

Introzzi, A. S., Cabanne, E. A., and De Soldati, L.: Plethysmographic Studies on the Action of Various Drugs on Caudal Flow of Blood. *Rev. argent. de cardiol.* 9: 230, 1942.

The plethysmographic method was applied to the study of variations in blood flow to the fingers caused by the intramuscular administration of nicotine acid, priseol, eupaverine and prostigmine to seventeen normal subjects and four patients with Raynaud's syndrome.

These drugs showed an inconstant effect on the finger's blood flow of normal subjects. The temperature of the skin rose markedly especially with eupaverine and priseol, and the central temperature generally decreased with nicotine acid.

In the patients with Raynaud's syndrome only prostigmine was found effective (two cases), though it should be studied in a greater number of subjects.

AUTHORS.

Sturnick, M. I., Riseman, J. E. F., and Sagall, E. I.: Studies on the Action of Quinidine in Man. II. Intramuscular Administration of a Soluble Preparation of Quinidine in the Treatment of Acute Cardiac Arrhythmias. *J. A. M. A.* 121: 917, 1943.

A soluble preparation of quinidine suitable for parenteral administration, containing 0.15 Gm. in each cubic centimeter, can be made by the addition of urea and antipyrine to quinidine hydrochloride. The preparation of this solution is not difficult, and the ingredients are readily available. Since this injectable quinidine can be stored in ampoules, it is of practical value in the emergency treatment of acute cardiac arrhythmias.

Twenty-four episodes of acute cardiac arrhythmias in a series of twenty patients were treated by the intramuscular administration of this preparation. In fifteen instances (thirteen patients) the rhythm was converted to normal. In three additional instances conversion to normal was probably due to this therapy. In one instance the dose used was too small. In the remaining five instances the drug failed to control the abnormal rhythm. Three of the five instances were attacks of sino-auricular tachycardia.

Toxic reaction to the drug (mild diarrhea) was experienced by only one patient. No local reactions were encountered.

The following appears to be a practical method for using the drug in the treatment of acute arrhythmias:

An initial dose of 0.45 to 0.6 Gm. should be given intramuscularly.

The response to each dose should be observed for one and one-half hours to two and one-half hours. If conversion to normal rhythm does not occur in that time, additional medication is indicated.

A favorable response consists in definite slowing of the apical heart rate, a rise in blood pressure to above the shock level, decrease in symptoms, or striking improvement in the patient's general condition. In such instances the initial dose may be repeated. If a favorable response is not observed, it is advisable to increase the size of the dose.

Injectable quinidine can be used whenever oral quinidine therapy is advisable. It is especially indicated when absorption from the gastrointestinal tract may be delayed or unreliable (vomiting, shock, and the like), and when rapid therapeutic action is desired.

Pearson, J. E. G.: Acute Disseminated Lupus Erythematosus: Recovery With Sulphanilamide. Brit. M. J. 1: 253, 1943.

A case of acute disseminated lupus erythematosus was treated successfully with sulfanilamide. The further trial of sulfanilamide therapy for the acute forms of this disease without clinical evidence of tuberculosis is suggested.

McCulloch.

Erratum

In the article entitled "Paroxysmal Supraventricular Tachycardia With A-V Block," by George M. Decherd, Jr., George R. Herrmann, and Edward H. Schwab, which appeared in the October, 1943, issue of the JOURNAL, volume 26, page 471, in the fourth line under Discussion "mechanism" should be changed to "interval."

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•Executive Committee.

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Original Communications

ON THE PATHOGENESIS OF THE SIGNS OF TRAUBE AND DUROZIEZ IN AORTIC INSUFFICIENCY. A GRAPHIC STUDY

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PROPER evaluation of acoustic phenomena in peripheral arteries is very important for the understanding of the hemodynamics of aortic regurgitation. Therefore, a series of observations based upon exact graphic records, and not on subjective appreciation, will be of some interest.

The acoustic phenomena in peripheral arteries in aortic insufficiency were studied a long time ago, mostly on the femoral artery.

In 1841, Bouillaud² described a double *murmur* in the femoral arteries of patients with this valvular disease. In 1861, his pupil Duroziez⁴ emphasized the significance of this double murmur (double *souffle*). He studied the conditions of its appearance (marked compression with the stethoscope) and emphasized it so that it was accepted as a typical sign of aortic regurgitation.

A few years later, Traube^{22, 6} described a double *tone* (Doppelton) which can be heard in rare cases by applying the stethoscope lightly on the femoral artery, so that the diameter of the vessel is not modified by the compression.

The fundamental work of Duroziez and Traube made many points clear concerning the causation of these murmurs and sounds.

1. The double tone is a rare phenomenon, the double murmur is frequent (Traube).

2. The double tone is a spontaneous phenomenon in the arterial wall (Traube). The double murmur, on the contrary, is an artificial phenomenon caused by eddies in the blood stream produced by compression with the stethoscope (Duroziez, Traube).

3. If the stethoscope is lightly applied on the artery, it is also possible to produce the first murmur by compressing the vessel *above* the stethoscope. The appearance of the second murmur, on the contrary, is favored more by compressing the vessel below it (Traube²²).

4. Neither phenomenon is typical of aortic regurgitation. The double

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tone, can be observed during fever (Fränztel,⁶ Traube²²), and the double murmur in typhoid fever, chlorosis, and saturnism (Duroziez⁴).

These observations afford a clear distinction between the two vascular phenomena, in spite of the confusion introduced by later workers.

The first arterial murmur was explained as caused by the eddies which are formed by the pulse wave under the narrow arterial section where the stethoscope is applied.

The first of the two sounds described by Traube seemed to be caused by the quick distension of the artery, because of the typical character of the pulse (pistol-shot sound). On the contrary, the second sound and the second murmur were differently explained, and numerous investigations were made in order to ascertain their meaning.

The second *tone* described by Traube was explained by him as caused by the rapid change of tension of the arterial wall after the quick distension.

The second *murmur* was explained by Duroziez as caused by a backward wave coming from the periphery. His own words were: “. . . le sang de tout l'arbre artériel, arrêté par la contraction des artérioles, réoule et, rencontrant à son tour un rétrécissement, il souffle comme il a soufflé en avant. . . . Les deux souffles vont en sens contraire; c'est un mouvement de va-et-viens.”

A few years later Toussaint and Colrat²¹ advanced the hypothesis that the second murmur was caused by the dirotic wave. Therefore, they admitted a double centrifugal movement of the blood stream under the stethoscope (double souffle en avant). The *centripetal nature* of the wave causing the second murmur was, however, admitted by all later authors. Since a total reflux from the periphery could not be easily visualized, the old theory was replaced by that of a local reflux. This would be caused by the marked difference in pressure in the two arterial sections which are separated by the stethoscope. This new concept was first advanced by Potain,¹⁷ then discussed and accepted by Ferrio and Bosio,⁵ and was further amplified by Gallavardin.⁷

The double femoral murmur is found in certain patients who do not have aortic regurgitation. Its occurrence in patients with conditions which accelerate the circulation was first observed by Duroziez.

Ferrio and Bosio,⁵ Tiee,²⁰ Laubry and his co-workers,⁹ and Blumgart and Ernestine³ studied it in patients without aortic insufficiency.

The studies of Ferrio, Laubry, and Blumgart need further discussion, because their observations are partly contradictory. Ferrio and Bosio⁵ found that the application of an elastic band to the leg may cause the appearance of a double murmur in the femoral arteries of normal people. The same device increases the double murmur of patients with aortic insufficiency.

Laubry, Brosse, and van Bogaert⁹ found that a peripheral obstacle, namely, a pneumatic cuff inflated nearly to the level of the systolic pressure, increases the intensity of the second murmur in aortic insufficiency. In arterial hypertension, compression below the stethoscope causes the

appearance either of a diastolic sound or a diastolic murmur. They confirm, therefore, the old observations of Traube. Quite different were the observations of Blumgart and Ernstene³ in their study of the double murmur in both the femoral and brachial artery. They found that applying a pneumatic cuff to the forearm and inflating it below the diastolic pressure abolished the second murmur in patients without aortic insufficiency (thyrotoxicosis, hypertension, normals). On the contrary, pressure with the upper edge of the stethoscope bell increased the murmur in the same patients. In patients with aortic insufficiency the second murmur was increased by the same pneumatic device and by compression with the lower edge of the stethoscope bell. In accordance with their own observations, Ferrio and Bosio, as well as Laubry, Brosse, and van Bogaert, believe that the second murmur is caused by backward flow in patients both with and without aortic regurgitation. Blumgart and Ernstene, on the contrary, admit a double mechanism: backward flow when there is aortic insufficiency, and forward flow when this condition is absent.

Summarizing the preceding studies, an increase in the intensity of the second murmur (and also of the second tone) was produced by applying a distal obstacle to the arterial flow in patients with aortic insufficiency. Contradictory results are reported on patients without aortic insufficiency; Blumgart and Ernstene observed disappearance of the murmur with a distal obstacle, but all others observed an increase (Traube; Ferrio and Bosio; Laubry, Brosse, and van Bogaert). As the former inflated the cuff below diastolic pressure, the latter much above it, the difference might be the result of using a different technique.

Further observations were made by Laubry and his co-workers⁹ concerning another murmur which may be caused by the second top of the pulse wave when there is anacrotism. In such cases there is a double murmur at first (main wave with anacrotic depression), and another murmur later (equivalent to the second murmur of Duroziez).

A few years earlier, a graphic study of the double murmur was made by Pasoli.¹⁶ In spite of a still incompletely developed phonocardiographic technique, he was able to record the first and second murmur. Among the chief results of his study were: (1) demonstration that there is no abnormal deformity of the pulse curve during the second murmur; (2) proof that, at the time of the second murmur, the pulse in the dorsalis pedis artery is still near the top. Pasoli admitted that the second murmur was caused by a second forward movement of the blood stream, produced by a local contraction of the artery.

TECHNIQUE

The acoustic vibrations of the arteries were recorded by means of a Stetho-Cardiette (Sanborn). This apparatus made possible a simultaneous recording of other tracings.

The first experiments were done with the original technique of Traube and Duroziez, but by substituting for the stethoscope, a microphone with an open funnel. Comparison was made between records with a stetho-

scopic microphone and those with a logarithmic microphone; the latter is more similar to the human ear. The audiophone enabled one to hear the sounds and murmurs during the taking of the records. A further study was made with microphones closed by a membrane which gives better tracings of high-pitched murmurs (Rappaport and Sprague¹⁸).

After ascertaining the type of murmurs and sounds which are typical of the femoral artery, attempts were made to obtain simultaneous recordings of sounds and arterial pulse at the seat of application of the stethoscope. This was done by using the special funnel and the crystal microphone described by Miller and White¹⁵ for venous pulse records.

Since it is very important to follow the pulse wave in its peripheral course after it has passed under the stethoscope, records were made in which the femoral sounds were recorded simultaneously with either a low tibial pulse or a foot pulse. The former was recorded by means of a pneumatic cuff and a new apparatus recently studied by Rappaport and Luisada.¹² A further problem, that of recording at the same time the femoral sounds and the heart sounds, was solved in the following way: Two absolutely identical Stetho-Cardiettes were used. One recorded Lead I of the electrocardiogram and the heart sounds over the aortic area. The other recorded Lead I of the electrocardiogram and the femoral sounds. The tracings were taken simultaneously at a film speed of 75 mm. per second. Both motors were started at the same time and simultaneous signals were written from time to time on both records. The signals made possible a comparison of the records. The ventricular complex of the electrocardiogram made possible an absolutely exact superimposition.

A similar technique was used for recording the arterial sounds either above and below a compression, or at different points of the femoral artery. A pneumatic cuff was applied on the limb. Two microphones were applied on the artery, above and below the cuff (Fig. 1B). In other experiments the cuff was displaced downwards, either just above or just below the knee. Two microphones were applied on the thigh. The upper compressed the femoral at the groin and produced the double murmur, and the lower was applied with just slight compression on the thigh. A test was made to ascertain that the latter was not producing any local murmur before starting the compression with the upper microphone (Fig. 1A).

The same technique was later used for the arm. Two Stetho-Cardiettes recorded the two phonoarteriograms simultaneously. Electrocardiograms and signals were recorded as mentioned above.

Later, two microphones were applied either 5 or 10 inches apart on the femoral artery. Two pneumatic cuffs gave the same light pressure to them. A test was made in order to exclude any local production of murmurs. Then another cuff was inflated to a high pressure below the lower microphone.

In a further series of experiments the changes induced by compression either above or below the seat of appearance of a murmur were investigated. For this purpose I used the apparatus described by Rappaport and myself¹² for blood pressure records. This contains a double microphone and is connected to a double pneumatic cuff. The upper cuff is inflated to a known pressure, and the lower cuff is connected to both microphones, giving two tracings, i.e., that of the pulse and that of the sounds. The device was employed in the routine way for the study of sounds and pulse below the compression. The order in which

the cuffs were applied was later reversed in order to study sounds and pulse above the compression (Fig. 1C).

This work was performed on twenty-two patients from different hospitals.* Eight of them had syphilitic aortic insufficiency, nine had rheumatic aortic insufficiency, and five had arteriosclerotic aortic insufficiency. Seven additional patients had arterial hypertension, and four subjects were normal students into whom different drugs were injected.

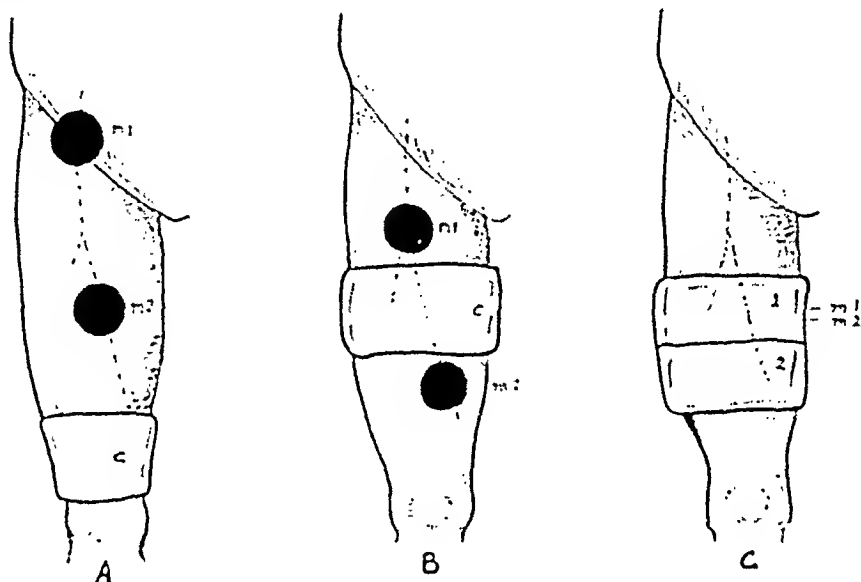


Fig. 1.—Different techniques for recording the femoral sounds above and below compression. *m1*, *m2*, microphones; *c*, cuff.

RESULTS

1. Aspects and Phase of the First Murmur.—The first murmur upon compression of the arteries is a constant feature which can be observed on normal people as well as on patients with aortic regurgitation. It starts slightly before the rise of the volume curve of the pulse and lasts during the ascending phase and slightly after the top. The first fact is due to eddies formed during the cessation of collapse of the artery which is closed by the compression (Fig. 2A).

The aspect of this murmur changes, depending upon the kind of microphone employed. It starts with a sudden multiple vibration, representing a snap, just before the dilatation of the artery. This is best recorded by a stethoscopic microphone. Then many multiple and high-pitched vibrations occur, which are best recorded by a logarithmic microphone (Fig. 2B and C). When the pulse wave has either a rounded ascending phase or an anaerotic depression, the first murmur lasts until the second top and slightly beyond it. In such cases a double murmur in the first phase is not unusual. When, on the contrary, the pulse wave rises abruptly and is followed by a rapid descent, the murmur lasts well beyond

*The Beth Israel Hospital, the Boston City Hospital, and the Medfield State Hospital. I wish to express my gratitude to Dr. H. L. Blumgart and Dr. M. D. Altschule, as well as to Dr. L. B. Ellis and Dr. Axelsson, for granting me the opportunity to study the patients.

the top. The average length of this murmur is 0.12 second. The maximal length was 0.20 second.

Records taken with the microphone of the blood pressure recording set showed a series of vibrations of a lower frequency, representing a very rough murmur. In general, the brachial shows a rougher murmur and slower vibrations than the femoral artery (Fig. 4).

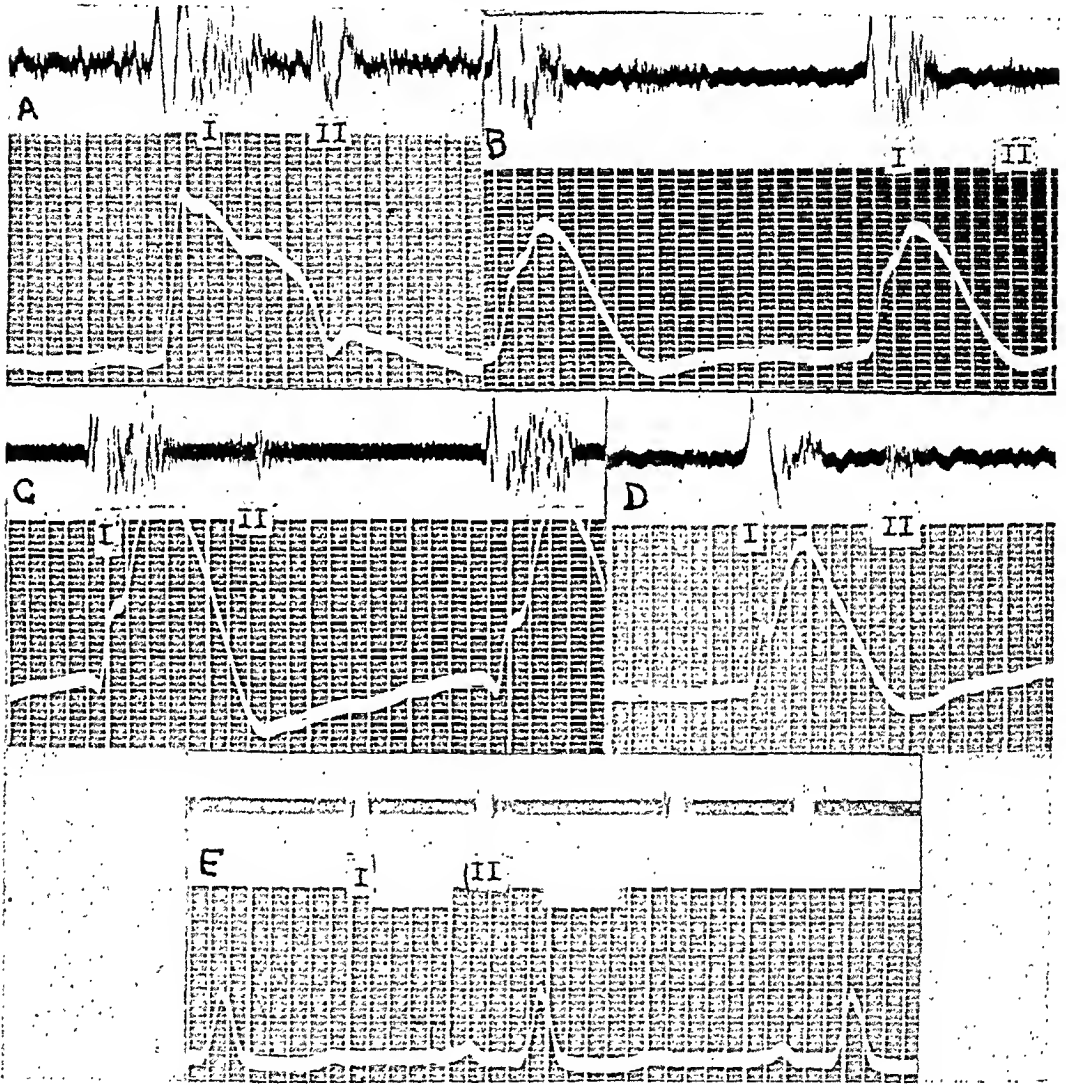


Fig. 2.—Femoral sounds and femoral pulse at the groin in different patients. The pulse is recorded at the site of compression. A, usual (stethoscopic) microphone; B, C, D, and E, special (logarithmic) microphone. A, Mitral and aortic regurgitation; B, syphilitic aortic regurgitation; C, double aortic defect; D, normal student after injection of 1 mg. of adrenalin; E, electrocardiogram and femoral sounds in a case of syphilitic aortic regurgitation. The femoral sounds were recorded by means of a logarithmic microphone, applied lightly above a cuff compressing the lower part of the thigh.

2. *Aspects of the Second Murmur.*—The aspect of the second murmur depends upon the microphone used. A stethoscopic microphone often shows a large and slow deflection, on which more frequent vibrations are superimposed (Fig. 2A). Marked individual variations were found. The murmur may be very short, consisting of only 5 to 6 quick vibrations,

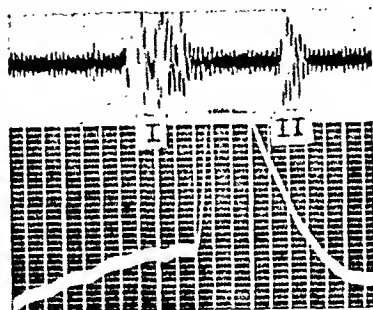


Fig. 3.—Femoral sounds at the groin and dorsalis pedis pulse in two cases of double aortic defect.

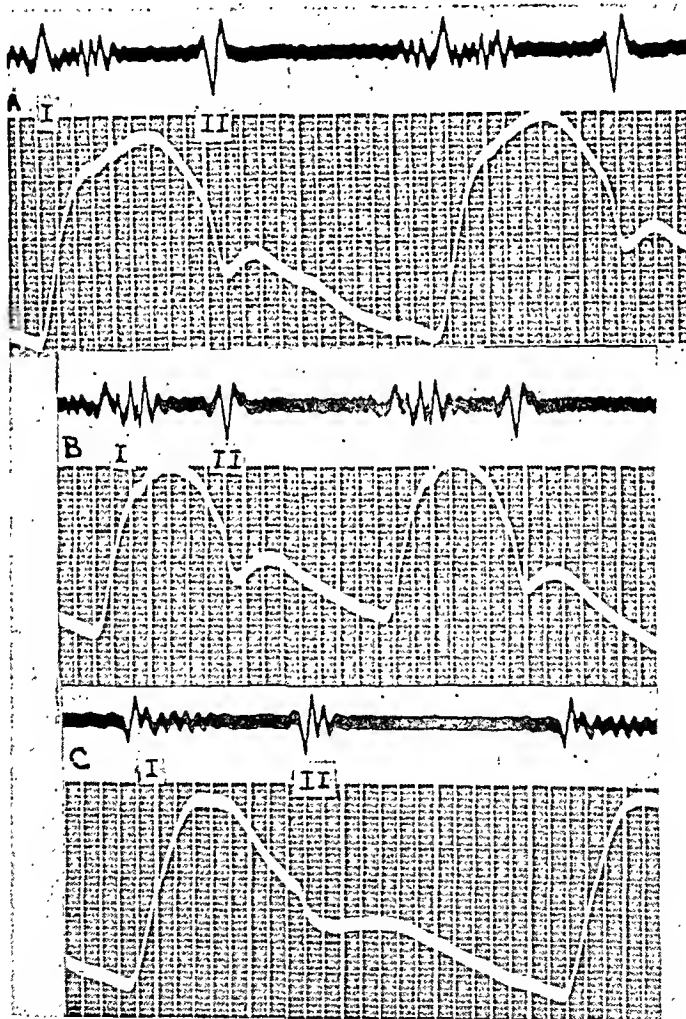


Fig. 4.—Brachial sounds and pulse recorded by means of the blood pressure recording set (like Fig. 1C, but inverted). A, Syphilitic aortic regurgitation (blood pressure 160/50; recording cuff, 30; compression, 140). B, Hypertension, no aortic regurgitation (blood pressure 165/80; recording cuff, 40; compression, 145). C, Normal student (after adrenalin, blood pressure, 140/60; recording cuff, 40; compression, 120). In all three the second murmur is represented in the records by a snap. At the femoral there was a double murmur.

and lasting 0.06 second. It may be much longer, lasting even 0.14 second. The murmur is usually shorter in the brachial and longer in the femoral artery. It may be represented only by a single or double vibration. In that case we should call it a snap, or a tone, not a real murmur. Tones are more frequently found in the brachial than in the femoral artery (Fig. 4).

3. *Phase of the Second Murmur.*—The second murmur in the femoral artery occurs some time after the second heart sound. In one case in which an exact measurement was made, a delay of 0.12 second from the beginning of the second aortic sound was found. In this case the second arterial murmur occurred when the maximal amplitude of the aortic diastolic murmur had already subsided. The comparative study was suggested by the desire to ascertain the exact relationship between second femoral murmur and phase of regurgitation, as evidenced by the diastolic murmur over the aortic area.

The second murmur in the arteries has a definite relationship to the shape and phase of the arterial pulse at the point of observation. When no appreciable diastolic wave was present in our records, and the pulse showed only an ascending and a descending phase, the second murmur occurred at the time of the lowest point of the descending phase. When a clearly defined diastolic wave was present, the second murmur occurred at the bottom of the depression preceding the diastolic wave. This occurred constantly, in the brachial as well as the femoral artery. When, instead of the murmur, there was a snap or tone, this also coincided with the depression preceding the diastolic wave (Fig. 4). Sometimes, however, this coincided with the descending phase of the main wave. When the murmur or tone was present in patients without aortic regurgitation, the same time relationship and the same connection with the phase of the pulse was found. When the murmur was a prolonged one, it lasted during part of the ascending phase of the diastolic wave.

Simultaneous registration of the sounds in the femoral artery and the pulse curve in the dorsalis pedis artery of the same side showed that the second murmur falls during the descending phase of that peripheral pulse, and sometimes is very near the peak of the pulse wave in that distant artery (Fig. 3).

A careful study which was made in order to ascertain whether any abnormal depression of the pulse curve coincided with the second murmur failed to reveal any.* This murmur is always present during the prediastolic depression. In one record, taken on the brachial artery, on the contrary, a small additional wave was found in the pulse curve at the time of the second murmur and during the prediastolic depression. This could be attributed, however, to an artifact.

4. *Pressure Necessary to Cause the Second Murmur.*—It is apparent that no exact evaluation of the compression is possible when this is

*Since the second murmur was attributed to abnormal pressure conditions caused by the stethoscope, theoretically it would be possible to observe an abnormal deformity of the pulse curve.

effected directly, either by the stethoscope or by the microphone. On the contrary, it was possible to ascertain it by the following device. A double pneumatic cuff was applied to the thigh, the lower part of which exerted a known pressure. The upper part recorded pulse wave and arterial murmurs under a very low inflation pressure (20 mm. Hg). This device was also found best for recording the double murmur (see later).

Studying the records at gradually increasing pressures shows that the second murmur starts approximately at a compression midway between systolic and diastolic pressure. The second murmur increases in loudness until the compression is 25 per cent lower than the systolic, and then decreases again. Complete obliteration of the peripheral tract of the artery causes disappearance of the murmur. The optimum compression seems to be, therefore, about three-fourths of the way up from the diastolic to the systolic. For instance, in patients with a pressure of 200/60, the murmur starts around 130, increases up to 165, and becomes fainter above that figure.

In most of the cases, the compression causing the murmur was also the best for obtaining a good pulse tracing in all its details. As is known, a good pulse curve is obtained with the oscillographs when the artery is compressed above the average arithmetic pressure and below the systolic. As confirmation of this, patients with a good diastolic wave showed the maximum height of this wave with the amount of compression which gave the best intensity of the second murmur. This was true for the brachial, as well as for the femoral artery, and was also true in patients who had the second murmur, but no aortic regurgitation.

5. Conditions Favoring the Appearance of the Second Murmur.—Comparison of the stethoscopic records taken *above* and those taken *below* the compression of a pneumatic cuff shows how the obstacle may influence the murmur. In patients with aortic regurgitation the murmur was always clearer and better in the microphone above, than in that below, the compression (Fig. 5). It was not unusual to see and hear a double murmur above, and a simple sound (equivalent to the first murmur) below, the compression. Patients without aortic regurgitation showed exactly the same behavior.

A rapid peripheral circulation and a high pulse pressure were the conditions under which the second murmur was found, even without aortic regurgitation. The pulse curve above the compression showed an increased diastolic wave, and that below the compression showed none. Records taken above a compression, but at different distances from it, showed that the murmur starts about 10 inches above a compression cuff, but becomes louder and louder until the immediate vicinity of the cuff is reached.

6. Transmission of the Murmur and Direction of the Blood Flow Causing It.—In all records taken on the femoral artery by means of

two microphones, the first murmur was recorded slightly later with the second microphone than with the first. The delay of 0.02 to 0.04 second was simply the time necessary for the pulse wave to reach the second microphone.

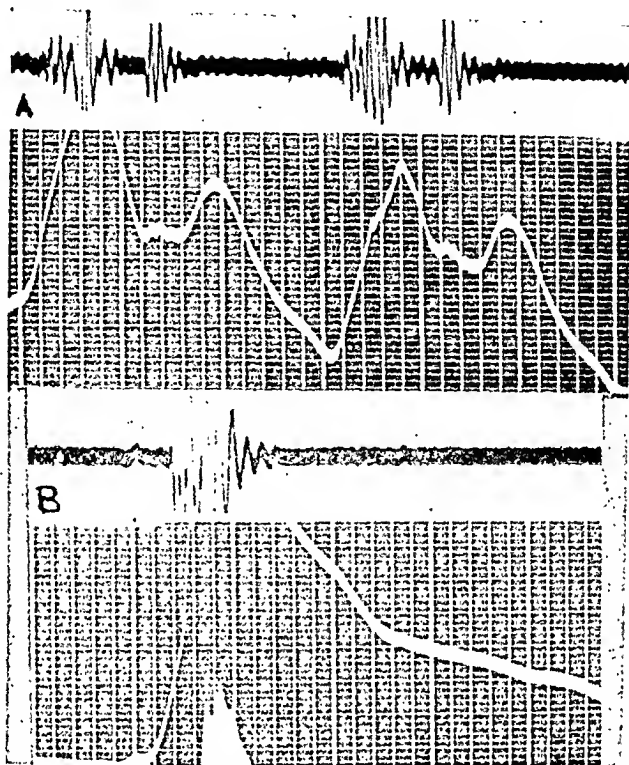


Fig. 5.—Double murmur recorded at the thigh by means of the blood pressure recording set (like Fig. 1C, but inverted). A, Records above the compression; B, records below the compression; (blood pressure, thigh, 250/80; recording cuff, 20; compression, 180).

In practically all femoral records the second murmur also occurs later on the second microphone (Fig. 6). The delay between appearance on the first and second microphones varies from 0.02 to 0.04 second. The different distance between the two microphones and the different speed of the pulse wave in different patients explain the different results obtained. The delay between the two second murmurs is sometimes equal to that between the two first murmurs, but is usually slightly longer. The records taken on the arm did not give such definite results; in most of them both murmurs were simultaneous. Only in a few of them was a minimal delay present, and then in the same sense as in the thigh. However, even in the arm, no precession of the second murmur was ever recorded in the upper microphone.

DISCUSSION

Our study gives exact data about the second murmur of Duroziez's sign. This murmur is actually linked to a definite phase of the pulse wave, for it occurs between the main wave and the dicrotic wave. Conditions for its occurrence are, first, a high pulse pressure, and, second, a high dicrotic wave. Every condition which increases the previous two

will either cause the appearance, or increase the intensity, of the second murmur. Compression of the artery at a level between average pressure and systolic pressure increases the height of the dirotic wave at the seat of compression and above it, and decreases the dirotic wave below it. The same compression causes appearance of the second murmur at the seat of compression and above it, but does not cause any murmur below it.

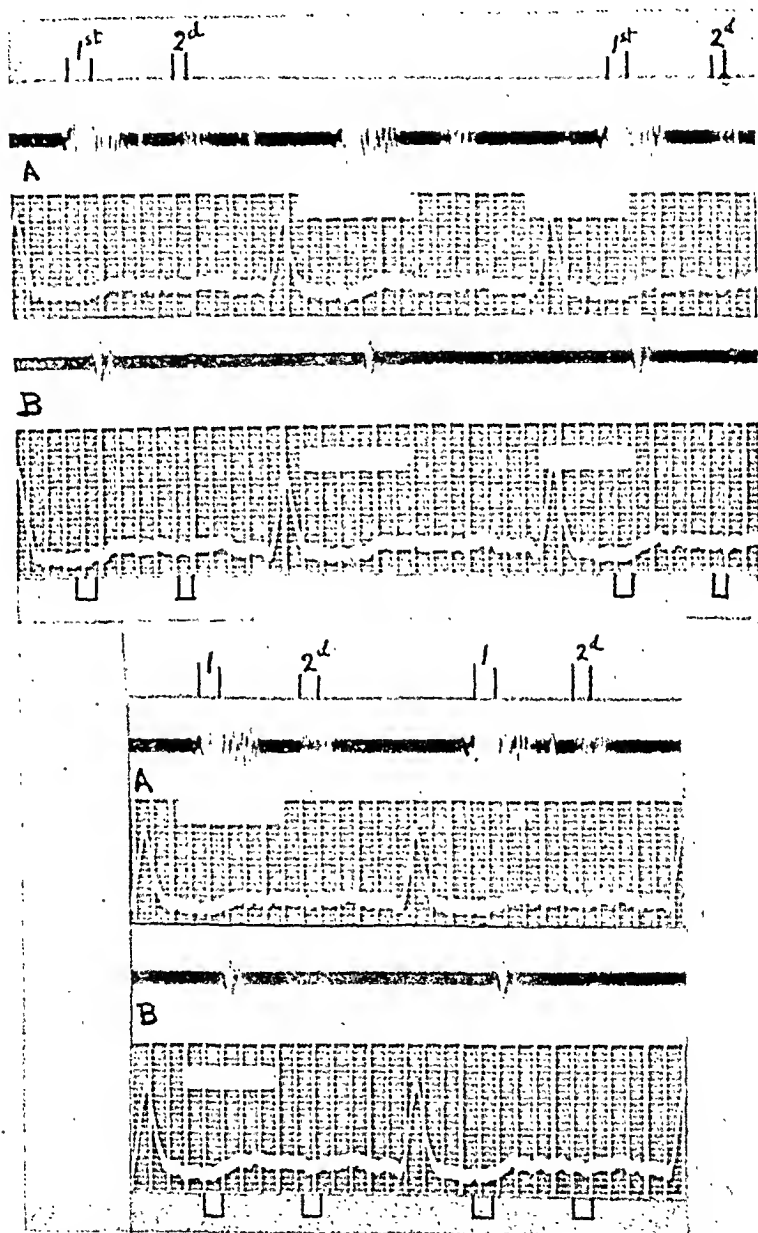


Fig. 6.—Delay between the first and second murmur, shown by placing two microphones 10 inches apart. A, Upper microphone over the groin (compression); B, lower microphone lightly applied over the thigh; a compression cuff is applied below the knee. The lower microphone does not record any murmur when no compression is applied on the upper microphone (Fig. 1A).

This is true in patients both with and without aortic regurgitation. Drugs which stimulate the circulation and increase the pulse pressure may cause the appearance of the second murmur in normal persons. There is a general unity of view in admitting that both murmurs of Duroziez's sign are caused by eddies in the blood stream. Since "fluid" murmurs radiate in the direction of the blood stream which causes them, the time of appearance of the murmur at different points along the femoral artery should give a clue about direction of the blood flow during the murmur. As a matter of fact, our records show that the second murmur occurs slightly later in a more peripheral part of the artery than in a more central. This is evidence that the blood flow is centrifugal at the time of the murmur.

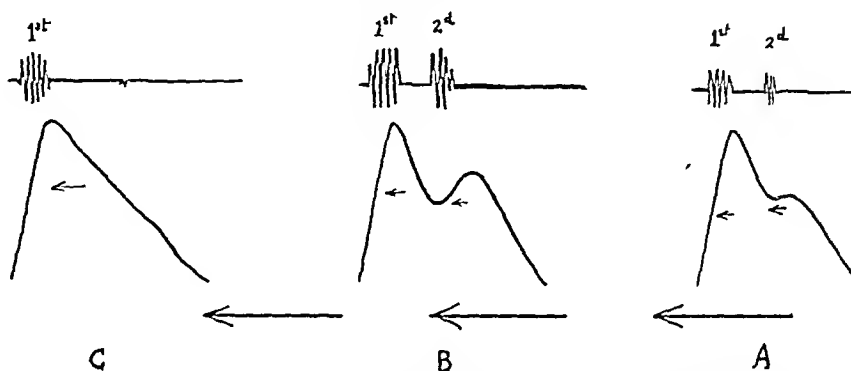


Fig. 7.—Sketch of the changes of the pulse curve and of the arterial sounds in passing under a compression. A, Above the compression; B, at the seat of compression; C, below the compression. The direction of the blood flow is from right to left.

The delay between the vibrations of the second murmur when it is recorded at different points along the same artery is often slightly longer than that between the vibrations of the first murmur. This fact points to a slower speed of the stream during the second murmur, in contrast with that during the first.

A definite explanation of the phenomenon cannot avoid taking into account the nature of the dirotic wave. When ventricular systole ends, and pressure eddies cause closure of the aortic valve, a rebound of the aortic wall forces the blood centrally as well as toward the periphery. In aortic insufficiency this rebound is much greater, and enables the pulse wave to follow its peripheral course in spite of regurgitation of blood which probably affects directly only the initial part of the arterial tree.

Under normal conditions the swing of the blood column towards the heart sets up a negative wave which travels toward the periphery behind the main wave, and is represented by the predicrotic notch of the pulse curve. In patients with aortic regurgitation there is no reason for admitting any other mechanism. In spite of the valvular incompetence, the aortic valves still represent an obstacle, and this is increased by the muscular tonus of the infundibular part of the left ventricle. Records taken on different arteries of patients with aortic regurgitation show

that the predierotic notch occurs later in peripheral than in central arteries. This shows that the negative wave has a centrifugal course. After closure of the aortic valves the blood column rebounds abruptly from their surface and sets up a second positive wave which will follow the predierotic notch toward the periphery. Here, also, there is no fundamental difference between patients with aortic insufficiency and others. The initial phenomena are further influenced by the action of the peripheral arteries, which deepens the predierotic notch and rounds out the dierotic wave.

The speed of both the predierotic notch and the dierotic wave is slightly less than that of the main wave, and this is true also of patients with aortic insufficiency, as demonstrated by records of sundry authors and our own.

In these patients we have, therefore, a double centrifugal wave, interrupted by a short phase in which the blood has lower pressure and lower speed, in spite of its centrifugal direction. The compression exerted by the stethoscope does not fundamentally affect these facts except as follows: in the proximal section the obstacle increases the height of the main wave, the depth of the predierotic notch, and the height of the dierotic wave; in the distal section, on the contrary, only the main wave is still present, for the dierotic wave has been flattened. In other words, the optimal pressure to cause the second murmur is that which allows free passage to the top of the main wave, but blocks the flow of blood during the predierotic notch. When the dierotic wave meets the obstacle, it rises in height, and then filters gradually below it, and loses its individuality. When the blood at the level of the dierotic wave meets the conical end of the artery above the compression, it forms eddies, and a murmur arises. As this blood filters gradually under the compression, the individuality of the wave is lost. No real murmur is recorded in a more peripheral section if the compression is extended over a long stretch. This explanation is confirmed by the fact that, when the main wave has a double top, separated by a depression (anaerotism), a double murmur occurs in the first phase, followed by a later murmur in the second phase. Complex polyerotic pulse waves sometimes produce a complex stethogram, with more short murmurs in the second phase.

Complete distal occlusion of the artery would prevent a centrifugal course of the main wave. This wave would still cause a first murmur under the stethoscope. After it, however, a slow backward flow, meeting more and more blood arriving from the center, would cause turbulent eddies, but no definite flow and no second murmur.

We shall now discuss the affirmed fact that the second murmur is increased by a distal compression, and that the first murmur is increased by a proximal one. As a matter of fact, only the first part is true, because the first murmur is increased by either a proximal or a distal compression. The reason is simple. The first murmur is caused by a large pulse wave, the main wave. Even passing under a compression, the blood flow is not markedly decreased, so that it is still able to cause

eddies after the obstacle. On the contrary, the second murmur is caused by the dirotic wave, which is smaller and less sharp. As it meets the obstacle it becomes flat and nearly disappears, so that no appreciable eddies are formed after the obstacle.

The explanation of Pasoli,¹⁶ who attributed the second murmur to arterial contraction, cannot be either proved or disproved here. If a tonic reaction occurs in the peripheral arteries and moves toward the periphery following the dilatation caused by the main wave (Hürthle,⁸ Mareš,¹⁴ Roncato,¹⁹ Luisada^{10, 11, 13}), this is likely to occur in the phase of the predierotic notch. The peripheral progression of this reaction would increase the height of the dirotic wave. Every obstacle causing a higher main wave, a deeper predierotic notch, and a rise of the dirotic wave would be accompanied by a stronger tonic reaction. Therefore, the second murmur of Duroziez can be explained by the theory of peripheral arterial contraction, but also in a much simpler way, as shown above.

The explanation of the second murmur in patients without aortic insufficiency is similar to that now advocated for patients with aortic insufficiency. The reason why Duroziez's sign is much more frequent in patients with aortic insufficiency than in others is very simple, and has already been advanced for many other arterial signs of aortic regurgitation.

High pulse pressure and high centrifugal speed of the pulse wave are found in the following conditions: (a) aortic regurgitation; (b) aortitis and atherosclerosis of the aorta without incompetence of the aortic valve; (c) hypertension; (d) hyperthyroidism; (e) fever. In most of these patients there is also a high dirotic wave, in spite of the traditional belief that the dirotic wave is very small in patients with aortic regurgitation. As a matter of fact, the point is that the rapid collapse of the arterial wall makes an exact record of the dirotic wave more difficult to obtain in such patients. High speed and a high dirotic wave also occur in cases of anemia.

The same categories of patients show Duroziez's sign in a decreasing order of frequency. Drugs which increase the pulse pressure and the tonic reaction of the arteries, like adrenalin, may cause the appearance of the double murmur in normal people.

In conclusion, the second murmur is caused by a centrifugal flow of blood, that of the dirotic wave, which meets an obstacle and slowly passes below it. The old idea of Toussaint and Colrat²¹ is, therefore, confirmed. The theory of backward flow is disproved by the following facts:

- a. No deformity of the normal pulse curve is caused by the obstacle in the section where the murmur arises.
- b. No deformity of the pulse curve is caused by the obstacle in the distant parts of the arterial tree.
- c. No distal precession of the murmur is found when it is recorded simultaneously in two sections of the same artery.

The second murmur is often replaced, on records, by a sound, snap, or tone. This has exactly the same phase in comparison with the pulse wave as the second murmur. The mechanism of its production is similar to that of the second murmur, but not identical. The diastolic wave meets with a section of artery which is completely occluded, and causes a snap of the wall. However, this cannot be the explanation of the sign of Traube. The double sound described by him occurs only rarely, and only when a slight compression of the stethoscope is exerted. The explanation of Traube, namely, that of a double snapping of the arterial wall suddenly dilating and suddenly collapsing, seems logical and still valid.

SUMMARY

1. A graphic study was made of the double murmur of Duroziez. Phonoarteriograms, electrospychmograms, and other tracings were recorded on patients with aortic insufficiency and on others who had the clinical sign of a double arterial murmur upon compression.

2. The exact phase of occurrence of the second murmur has been ascertained. This is at the time of the prediastolic notch.

3. The best external pressure for the appearance of the second murmur has been studied. This is about three-fourths of the pulse pressure above the diastolic pressure, and coincides approximately with the level of the depression preceding the diastolic wave.

4. The second murmur also occurs without compression at a certain point if compression similar to that reported above is made on a more distal section of the artery.

5. The obstacle presented either by the stethoscope bell or by a pneumatic cuff causes different changes above and below. Above the obstacle the prediastolic notch becomes deeper and the diastolic wave becomes higher. Below the obstacle the diastolic wave is more flattened, and may disappear. Above the obstacle the second murmur is sharp and distinct. Below the obstacle the murmur is either indistinct, or is represented by a dull snap, or is missing. This was true in patients both with and without aortic insufficiency.

6. The pulse tracing fails to reveal any abnormal deformity at the site of appearance of the second murmur. Also no deformity is found in the more peripheral pulse, in spite of the fact that the phase of appearance of the second murmur is often near the top of the main wave in the dorsalis pedis artery.

7. Simultaneous stethographic records at two points on the same artery fail to show an earlier appearance of the second murmur in the more distal section. As a matter of fact, they show a later appearance in that section, which demonstrates a peripheral blood flow during the occurrence of the second murmur.

8. Drugs which stimulate the circulation may cause the appearance of the double murmur of Duroziez in normal persons.

9. For all of the preceding reasons, a backward flow of blood during the second arterial murmur is denied, and a forward flow is admitted. The conditions of appearance are discussed, and a common explanation of the mechanism is furnished for both patients with and without aortic insufficiency.

10. The mechanism by which the sign of Traube is produced is further discussed.

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A FREQUENT OBSTRUCTIVE ANOMALY OF THE MOUTH OF THE LEFT COMMON ILIAC VEIN

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WHEN performing an autopsy, one of the last acts of the pathologist is to open and inspect the inferior vena cava and its tributaries. He first opens the right common iliac vein and then approaches the left. Although the right is usually easily opened, the left at times is difficult to enter, not only because of its position behind the origin of the right iliac artery, but because, as we have found, the mouth of the left common iliac vein is frequently obstructed by fibrous thickenings and adhesions. Since this anomaly is not generally known, but seems to be important in regard to thrombosis of the lower extremities, which is known to occur more frequently in the left than in the right leg, a study has been made, on unselected material, of the structure of the inferior vena cava and its bifurcation into the two common iliac veins.

Literature.—The literature on the pathology of the inferior vena cava and its tributaries deals chiefly with malformations resulting from improper formation or obliteration of the posterior and supracardinal veins. Obstruction of the mouth of the left common iliac vein seems to have been described only by McMurrich,^{1, 2} in 1906. If this observation remained unrecognized, it was probably because of the fact that the description was published only in abstract form.

In his second, more detailed, abstract, McMurrich states that he found an obstruction in 30 per cent of fifty-seven cases, and, with one exception, the lesion was in the left vein. There were three general types of obstruction, namely: (1) "A narrow thickening at the lateral border of the vein"; (2) a triangular adhesion at the lateral border of the vein, the base corresponding to the border, and the apex projecting toward the lumen; and (3) a columnar adhesion dividing the lumen into two portions and "occurring anywhere from the center of the lumen of the vein to within a millimeter or so of its lateral border." In one case an obstruction was observed in the right common iliac vein, and the lumen was double for a considerable portion of its course.

Considering the cause of the obstruction, McMurrich expressed the view that it seemed probable that it was a persistence of an embryonic condition. However, the relation of the lesions found to the ages of the subjects was not considered. As to the significance of the condition, he pointed to the fact that thrombosis of the iliac vein is much more frequent on the left than on the right side, and concluded "that in this adhesion may be found one of the contributory causes of the thrombosis."

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MATERIAL

After happening upon an obstructive lesion of the orifice of the left iliac vein (Autopsy 40789, Philadelphia General Hospital), and shortly after observing six additional cases among twenty-seven consecutive autopsies performed by the senior author, we undertook a systematic study of normal and obstructed iliac veins at various ages.

The veins were largely collected from the Philadelphia General Hospital but also from the Departments of Anatomy (Dr. Batson) and Pathology of the University of Pennsylvania. Included in this series was a case of situs inversus of the lower vena cava (Autopsy 41870, Philadelphia General Hospital), and eleven adult cases which were used for microscopic study only.

The total number of veins studied by us amounted to 412. Of these, 264 were from adults, 23 from adolescents 10 to 20 years of age, 28 from children 1 to 9 years of age, and 97 from stillborn babies and infants ranging from 21 cm. in length (vertex to coccyx) to 10 months of age.

OBSERVATIONS

Of the 399 of these 412 veins that were suitable for statistical analysis, 282 (70.5 per cent) had an essentially normal appearance, 95 (23.8 per cent) showed definite obstructive anomalies, 16 (4.0 per cent) were possibly slightly obstructed, and 7 (1.8 per cent) presented some other changes.

Normal Appearance of the Opening of the Left Common Iliac Vein Into the Vena Cava.—Of 261 essentially normal veins which were studied by us in detail, 215 showed a valve at the lower pole of the mouth (Fig. 1). In the remaining 46 veins the valve was lacking; its absence was observed in:

0 of 79 stillborn babies and small infants	(0 per cent)
6 of 35 children from 1 to 16 years of age	(17.1 per cent)
6 of 51 adults from 19 to 49 years of age	(11.7 per cent)
18 of 63 adults from 50 to 69 years of age	(28.6 per cent)
16 of 33 adults from 70 to 90 years of age	(48.5 per cent)

46

A similar age distribution was found among 118 cases in which there were obstructive lesions, possible obstructive lesions, and other changes. In these cases, the valve was absent in 44:

1 of 18 stillborn babies and small infants	(5.5 per cent)
3 of 14 children from 1 to 16 years of age	(21.4 per cent)
13 of 33 adults from 19 to 49 years of age	(39.3 per cent)
15 of 36 adults from 50 to 69 years of age	(41.7 per cent)
12 of 17 adults from 70 to 90 years of age	(70.6 per cent)

44

Textbooks of anatomy and pathology rarely give information about a valve at this point; some say that there is none, and others that it may sometimes be found. Our figures can be taken only to indicate that there is normally a valve at the mouth of the left common iliac vein, and that it is "worn off" in many persons with advancing age, and presumably worn down in still more. Now, if this valve is worn down, there is good reason to believe that other valves, such as those of the femoral veins, may also be worn down. This is significant in regard to the cause of varicose veins of the lower extremities, which are often explained as a result of venous valvular insufficiency.

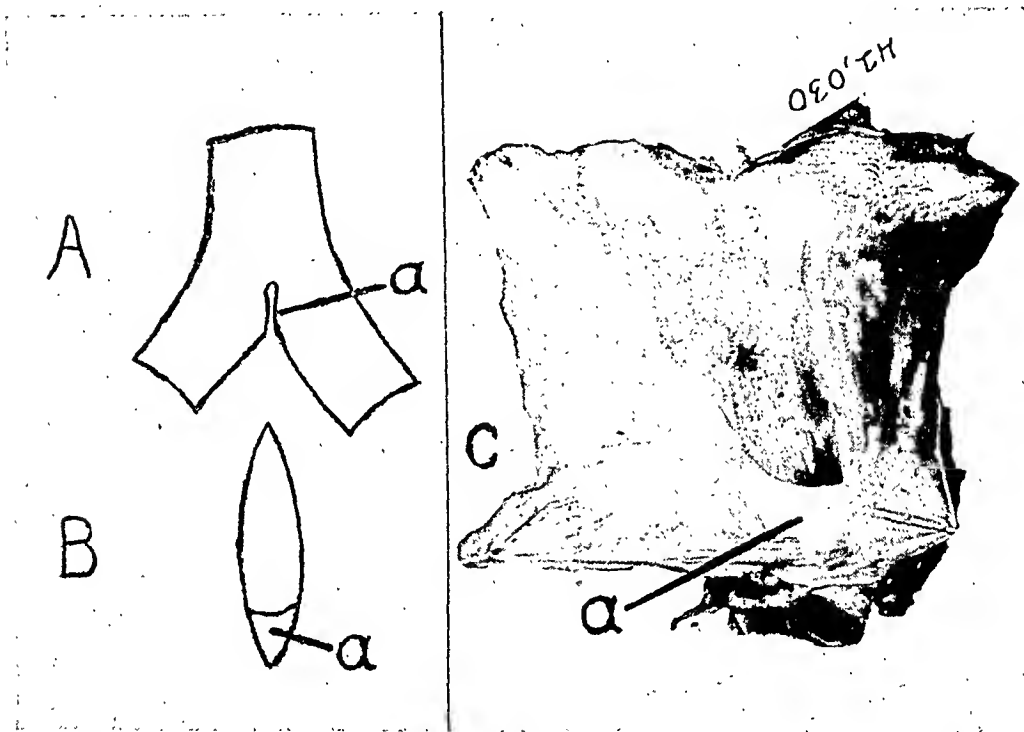


Fig. 1.—Normal opening of left common iliac vein into the inferior vena cava, with valve at lower pole (a). A, Anteroposterior view; B and C, lateral view (after opening inferior vena cava and right iliac vein) towards mouth of left common iliac.

The "Width" of the Orifice of the Left Common Iliac Vein.—This was ascertained by measuring the length of the longest axis; the orifice was held open by a pair of compasses without more traction than that required to get a smooth surface. This measurement was found to rise from about 2.5 mm. in the fetus measuring 21 cm. from vertex to coccyx, to about 7 mm. in stillborn babies measuring 40 cm. (Fig. 2A). After birth, it rose at first rapidly and later more slowly, to 20 mm. at about 15 years of age, and 24 mm. during the seventh decade. Thereafter it declined again (Fig. 2B). The fact that four infants from 1 to 21½ months of age showed a considerably smaller width than others of their age is obviously due to premature birth of these babies. This could be

confirmed in the case of one infant, 11½ months of age, which was only 30 cm. long (vertex to coccyx), for this is the length of the fetus in the eighth intrauterine month.

It may be mentioned here that there were no differences in the width of the mouth of the left common iliac vein or in the frequency of absence of the valve in relation to the subject's color or sex.

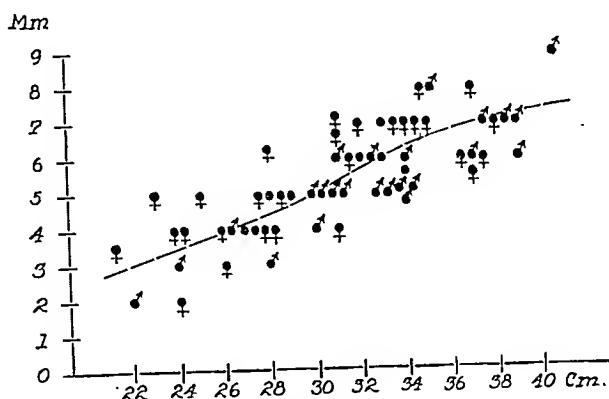


Fig. 2A.

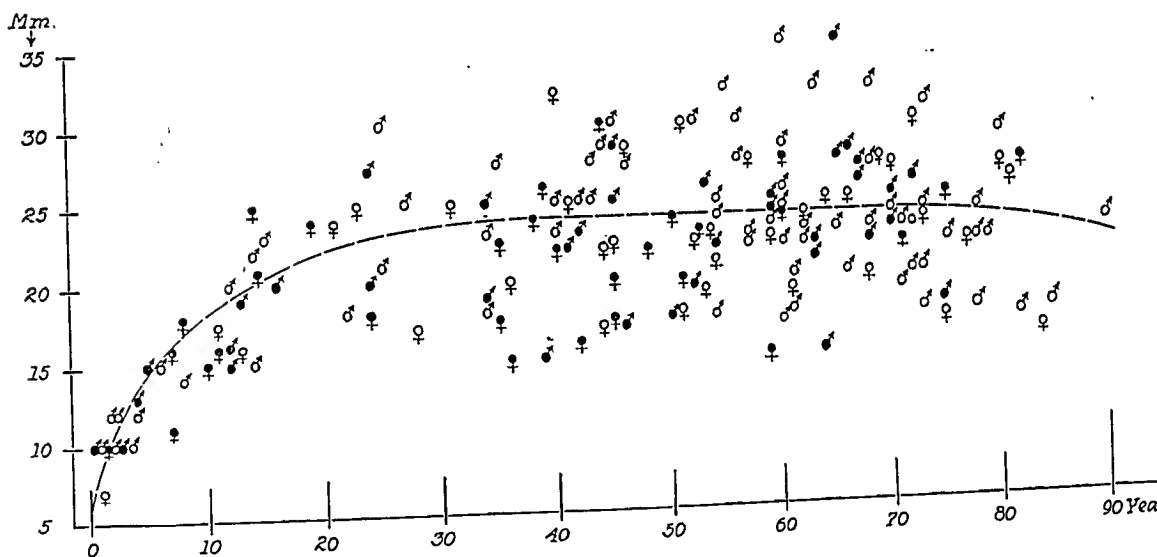


Fig. 2B.

Figs. 2A and 2B.—Chart of the width of the mouth of the left common iliac vein in relation to sex, color, and age. (A, In fetal life; B, in children and adults. In the latter curve, B, the open white symbols refer to white people, and the solid black circles to Negroes; whereas, in curve A, the white circles refer to both white people and Negroes.)

The Morphologic Appearance of the Obstructing Lesion.—According to their localization and other criteria, the lesions could be divided into five groups. Group I showed all transitions from “a narrow thickening” to triangularly shaped areas obstructing the upper pole of the mouth (Figs. 3, I and 4, I). Group II showed essentially the same picture except that all exhibited a channel passing along the left wall of the vein (Figs. 3, II and 4, II); and some also had one or several additional channels passing through the main portion of the obstructing

lesion (Figs. 3, II and 4, II). Group III included several varieties of adhesions dividing the lumen into two more or less equal portions (Figs. 3, III and 4, III). Some of these showed narrow bands (Fig. 3, III), whereas others showed membranes or triangular areas (Fig. 3, III). The latter were arranged either in the plane of the orifice (Fig. 3, III, second from left), or were perpendicular to it (Fig. 3, III, fourth and

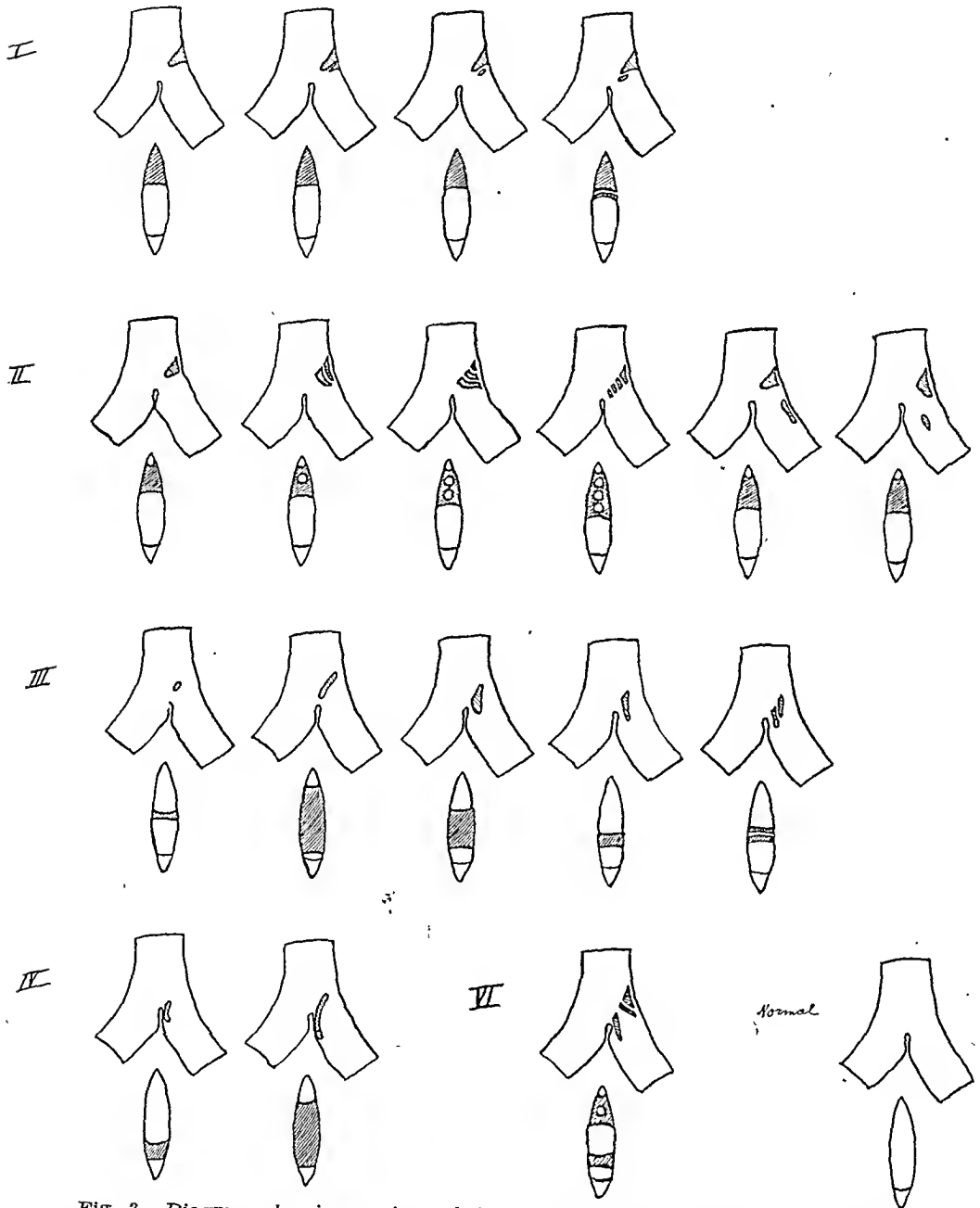


Fig. 3.—Diagram showing various obstructions of the mouth of the left common iliac vein as seen in the anteroposterior view and in the lateral view (from inferior cava and right iliac towards mouth). Nos. I to IV refer to the various groups of obstructions as described in the text; miscellaneous Group V obviously cannot be represented by a single figure; No. VI is a combination lesion of II and III.

fifth from left). Group IV included adhesions at the lower pole of the mouth, showing a tendency to extend behind the valve (Figs. 3, IV and 4, IV); and Group V included miscellaneous lesions, most of which were characterized by multiple irregular bands (Fig. 4, V); one showed such an extensive obliteration of the orifice that at no place could a probe be inserted, and water filtered through very slowly (Fig. 5, B). Yet just below the orifice the vein was patent and smooth-walled (diameter, 8 mm.). Some showed remnants of thrombotic material (Fig. 4, Vx). In one case, finally, a combination of Groups II and III was observed (Fig. 3, VI).

Of our obstructions, 38 belonged to Group I, 23 to Group II, 12 to Group III, 9 to Group IV, and 13 to Group V (Table I). The upper pole of the opening thus appears to be the seat of obstructions more frequently than the lower pole.

TABLE I

FREQUENCY OF THE VARIOUS OBSTRUCTIVE LESIONS; WITH FREQUENCY OF ABSENCE OF VALVE

TYPE OF OBSTRUCTION GROUP	WITH VALVE	WITHOUT VALVE	TOTAL
I	18	20	38
II	12	11	23
III	6	6	12
IV	8	1	9
V	5	8	13

The width of the lumen of the left common iliac vein immediately below the obstructions of the orifice was not materially altered by their presence, except in Autopsies 41397 and 41798, in which orifice and lumen were so narrow that a probe measuring 2 mm. in diameter could be forced through only with difficulty (Fig. 4, Vy). It can be assumed that this observation depends on such factors as the age at which the lesion became obstructive and the nature of the collateral circulation that developed.

There was no persistence of a left posterior cardinal vein or supra-cardinal vein in any of the cases in which this possibility was investigated.

As to the valve at the lower pole of the opening, Table I indicated that it was missing in 48 per cent to 58 per cent of the cases in all groups except Group IV, in which it was absent in only 11 per cent. The frequent absence of the valve in the presence of obstructions seems to be well explained by the greater stress and strain to which such a valve is exposed, and, in extreme cases, to obliteration of the valve by the sclerotic process. As to the less frequent absence of the valve in Group IV, aside from the small number of cases in this group, the explanation may be due, not to the youth of the persons involved, for the average age of this group amounted to over 60 years, but to the fact that the

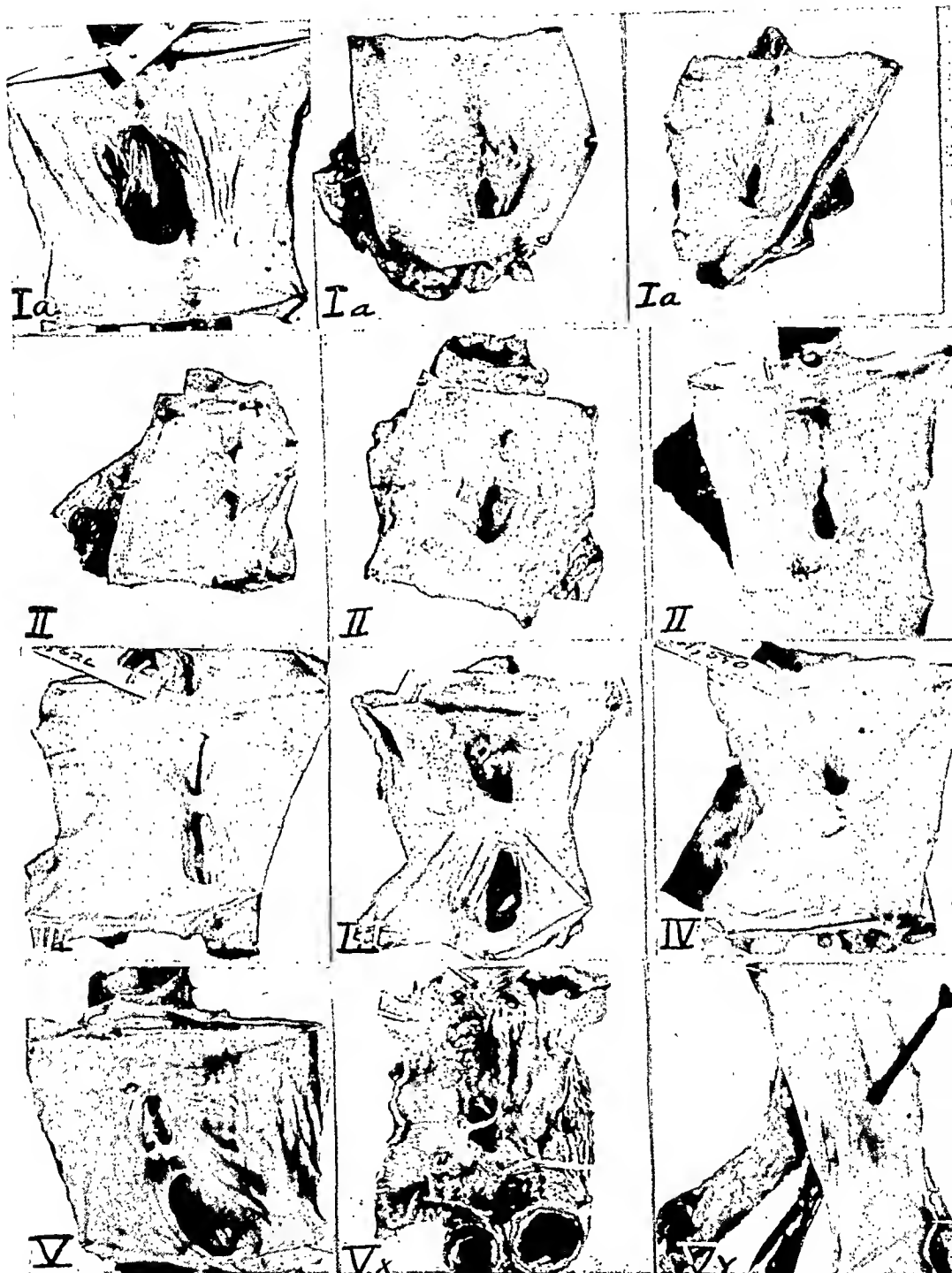


Fig. 4.—Various obstructions of the mouth of the left common iliac vein as seen in the lateral view. Nos. I to V refer to the various groups of obstructions as described in the text.

obstructing lesion in Group IV stands in the way of the bloodstream, which exerts stress and strain on the valve; that is to say, the valve is protected by the lesion. That this may be the correct explanation seems to be borne out by the fact that absence of the valve in this group occurred even less often than in our normal subjects of similar age (see figures in paragraph on the normal appearance).

Histology.—The microscopic appearance of our lesion seemed to be the same in most cases. There was a great deal of elastic tissue, and some collagenous tissue; smooth muscle cells were also present. On the other hand, inflammatory cell infiltrations were not observed, nor was the irregular arrangement of scar tissue found.

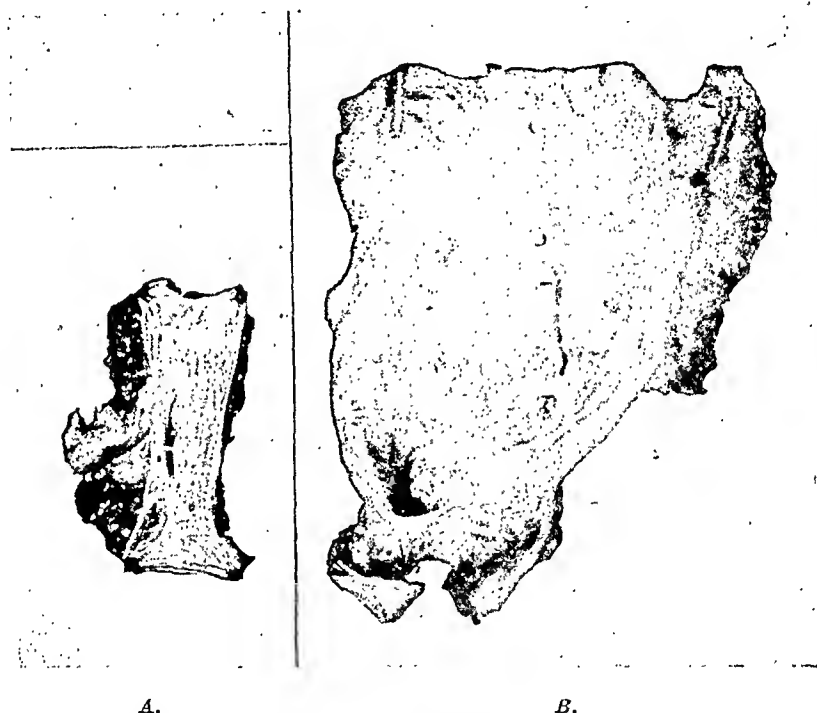


Fig. 5.—A, Obstruction of the mouth of the left common iliac vein in a newborn baby measuring 31 cms. in length (Group III, No. 9). B, Obstruction so great that probe could not be inserted and water barely filtered through (male, 9 years of age, University of Pennsylvania Hospital, Autopsy '43—318).

The Age Distribution of the Obstructing Lesion.—After the first decade, the obstructing lesion was found in 33.8 per cent of all our cases (Table II). There was no significant difference in incidence of obstruction between any of these age groups after the first decade, and there was no significant age difference in the relative frequency of the obstructions analyzed according to groups. Among our stillborn babies and children up to 10 years of age, we found only six cases (4.7 per cent) of definite obstructions. These belonged to Groups I, II, III (Fig. 5), and IV. However, in this group of stillborn babies and children up to 10 years of age, sixteen possible obstructions were observed at the upper

pole of the orifice; the entries in the protocols read: "Probably adhesion at upper pole," "fold at upper pole resembling adhesion," etc. If we add these to our number, the frequency in stillborn babies and infants up to 10 months rises to 17 per cent, and that of children from 1 to 10 years, to 26.3 per cent. These small, delicate vessels must be seen to realize the difficulty in making correct decisions as to the presence or absence of obstruction.

Other Anomalies.—Changes other than obstructive lesions which were observed among our cases were: (1) An unusually large valve with a perforation at its lower pole (Autopsy 41810, 43 years, female, Negro; Autopsy 42101, 67 years, male, white); (2) low position of the valve (Autopsy 16, body 24 cm. long, anencephalus); (3) an unusually low bifurcation with absence of the valve (Autopsy 42580, 2 years, male, Negro); (4) absence of the common portion of the left common iliac vein, with two mouths at the bifurcation (Autopsy 12, body 30 cm. long); (5) complete fibrous obstruction of the lower section of the inferior vena cava between its bifurcation and the mouths of the renal veins, with the posterior rami of the lumbar veins markedly distended, compensatorily (Autopsy 46217, 68 years, female, white); (6) adhesions in the right common iliac vein as a part of an organizing thrombus (Autopsy 41561, 49 years, female, Negro); and (7) situs inversus of the lower vena cava (Autopsy 41870, 66 years, male, white).

Although the anomalies listed here under numbers 1 to 5 do not appear to have received attention, both numbers 6 and 7 have been previously recorded. Adhesions in the right common iliac vein were seen once by McMurrie^{1, 2} and situs inversus of the lower vena cava has been observed by a good many authors. Zunstein³ found situs inversus in 0.45 per cent of his cases, and Seib,⁵ in 0.56 per cent (for literature see Maxwell and Erwin⁴ and Seib⁵).

DISCUSSION

If we compare our observations with those of McMurrie, we find conformity as far as the frequency of the obstructions is concerned. Whereas McMurrie² observed a frequency of 28 per cent (in 57 cases), we found an incidence of 4 per cent to 17 per cent in babies up to 10 months of age; 9.7 per cent to 26 per cent in children from 1 to 8 years; and 33.6 per cent in all age groups beyond 10 years. (N. B. The wide range given in the younger groups is influenced by the large personal factor which enters into the decision when the veins are very small and flexible.) As to the morphology of the obstructions, our Group I corresponded to McMurrie's Types 1 and 2, and his Type 3 embraced our Groups II and III. Our Groups IV and V were not described by McMurrie.

Concerning the pathogenesis of the obstructions, McMurrie's idea¹ that they are probably the result of defective embryonic development

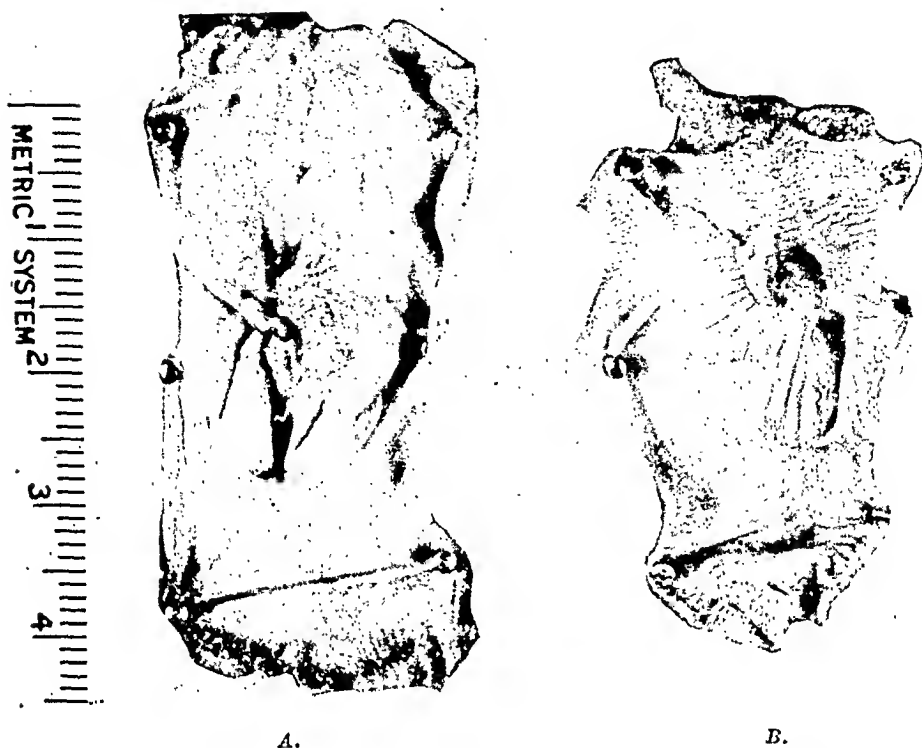


Fig. 6.—Recent obstructions of the upper pole of the mouth of the left common iliac vein in children 10 and 13 years old (Autopsies 43881 and 1056).

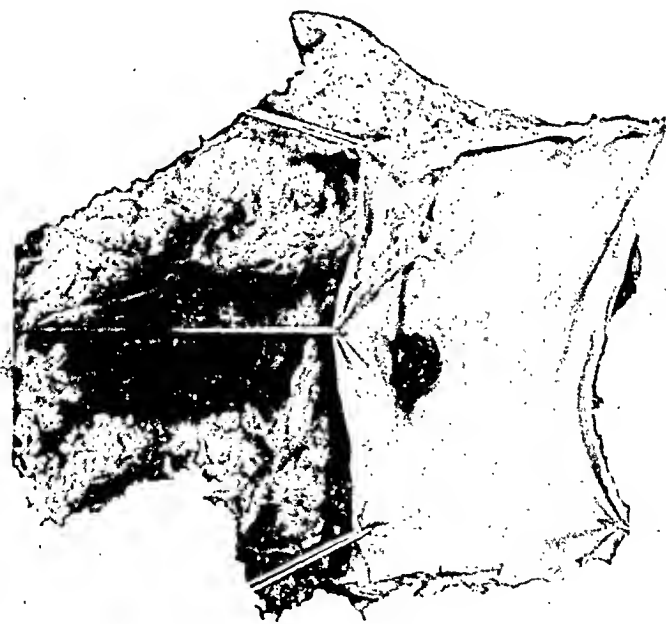


Fig. 7.—Thrombosis of the left common iliac vein in a case of obstruction of the greater portion of the mouth (Philadelphia General Hospital, Autopsy 41493).

is of interest in view of the closure of several segments of the left cardinal vein and the union of the left iliac with the vena cava by means of a developing communicating branch. The view is not supported, however, by our observations that only a few clearly developed obstructions are seen in the newborn and in children up to 10 years, whereas adhesions *in statu nascendi* were found in children as old as 10 or 13 years (Fig. 6). As a matter of fact, our observations seem to show that relatively few obstructions are formed during embryonic life, and that the great majority arise after birth. But since the frequency of adhesions in the second decade was as high as in the adult group, it may be concluded, with due regard to the small numbers available in the separate age groups, that most obstructions are acquired during development and growth, and that few, if any, are formed after the second decade.

As to the cause of the obstructions, it should be noted that most were located at a point where the right iliac artery crosses and exerts pressure on the left iliac vein. It is conceivable that this pressure interferes with the proper development of its orifice or causes an injury resulting in organization and fibrosis. (It should be noted, in evaluating this factor, that the relative positions of the arterial and venous bifurcations may change with age, and may be different during life from what they are on the autopsy table, according to the law that an elastic tube lengthens, as well as dilates, with increasing pressure.) That this pressure factor may be the correct explanation is further supported by the observation that no such obstructions have been found at the mouth of the left renal vein, the embryonic development of which from a segment of the left cardinal vein closely resembles that of the left common iliac; but here the aorta lies behind the vein.

Some of our obstructions were found to be organized thrombi. These are included in our Group V, although in not all cases of this group was the obstruction the outcome of thrombosis. Obstructions as a result of organization of thrombi differ from other obstructions in that they lack a definite pattern, show great irregularity in the arrangement of the individual bands of connective tissue, and show various transitions from early thrombosis to complete organization. In this group should be included, also, our only case of right-sided obstruction, for the thrombus which caused the proliferation of the connective tissue could still be identified.

Considering the clinical significance of our observations, we wish to discuss briefly the occurrence of thrombi in the iliac veins. Thrombosis in this location was observed in nine of our adult cases. In seven cases we found involvement only of the left side (Fig. 7); whereas, in the two remaining cases, both sides were involved. Of the seven cases in which there were thrombi in the left vein, there was partial obstruction of the orifice in four, and no obstruction in three. Since we have found that absence of this obstruction in adults is twice as common as its pres-

ence, it follows that, in our material, thrombosis of the left common iliac vein was more than twice as common in cases of obstruction than in those in which there was no obstruction.

In order to study this matter in larger numbers, the records of 1,000 consecutive recent autopsies at one of our hospitals were examined. In this series, pulmonary embolism was recorded 82 times. In these 82 cases, iliac vein thrombi were found 11 times. Furthermore, in 16 cases in which iliac vein thrombosis was recorded (in some of which there was no pulmonary embolism), the right common iliac vein was found to be affected 3 times; the left, 8 times; and both veins, 5 times. These figures show once more the preponderance of thrombosis in the left common iliac vein.

SUMMARY

This study of the opening of the left common iliac vein into the inferior vena cava is based on the examination of 412 bodies: 97 stillborn babies and infants up to 10 months old, 28 children from 1 to 9 years of age, 23 adolescents from 10 to 19 years of age, and 264 adults up to 90 years of age.

The width of the opening first increased rapidly with increasing age, and later more slowly. The curve reached its peak during the seventh decade.

A valve was found to be normally present in the newborn at the lower pole of the opening, but it appeared to be worn off in an ever greater percentage as age progressed, and more so in obstructed than in normal openings. This observation seems to be significant with regard to the cause of varices of the lower extremities, which have often been explained as a result of venous valvular insufficiency.

Obstruction of the orifice in the 399 cases analyzed was observed in 95 instances (23.8 per cent), with a possibility of 16 more instances in the stillborn and infants. It was less common in children and babies (4.7 per cent), although, if the 16 doubtful cases are included, the percentage rises to 17.3 per cent. In those over 10 years of age, it was found 89 times (33.8 per cent). It occurred with equal frequency in males and females, and in whites and Negroes.

According to location and other criteria, the obstructions could be divided into five groups (Figs. 3 and 4). The most common site of obstruction was the upper pole of the orifice, where two-thirds of all obstructions were found.

Concerning the pathogenesis of the obstructions, few, if any, were thought to be caused by faulty development, *per se*. They appeared to be acquired during the growth period, rarely before birth, and rarely after adolescence.

As to the mechanism involved, it was observed that the obstructions occurred at a point where the right iliac artery crosses and exerts pressure on the vein. This pressure conceivably interferes with the proper development of the opening into the vena cava or causes an injury resulting in organization and fibrosis. In a small number of cases the obstructions could be shown to be organized thrombi.

The clinical significance of the obstructions is apparent from the greater frequency of thrombosis in the left than in the right leg. This preponderance could be confirmed in our material, as well as in an analysis of 1,000 consecutive autopsies from one of our hospitals.

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DISSEMINATED ARTERIAL INTIMAL PROLIFERATION, WITH THROMBOSIS

REPORT OF A CASE

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IN 1879, von Winiwarter¹ described a disease of the peripheral arteries which he termed "endarteritis obliterans." Since that time a voluminous literature on the subject of vascular occlusive diseases has accumulated, and various theories have developed concerning the pathogenesis and essential nature of the lesion. In 1908, Buerger² criticized the term "endarteritis obliterans" and described a condition which he called thromboangiitis obliterans, outlining certain diagnostic criteria. Other authors, however, have since included under this name conditions which do not fulfill these criteria. It seems possible, therefore, that the term thromboangiitis obliterans has been used to denote more than one disease entity, and, consequently, the classification of vascular occlusive diseases has remained confused.

The present case belongs somewhere in this category, but, because of certain clinical and pathologic features, it defies accurate classification.

CASE REPORT

M. M., a 27-year-old, white housewife, was seen in March, 1941, when she complained of the symptoms commonly associated with congestive myocardial failure, namely, dyspnea, orthopnea, cough, hemoptysis, palpitation, tachycardia, pain in the chest, and edema. The onset of the present illness had been insidious, and much of the history prior to the first visit was obscure, except that she had consulted several physicians without definite improvement in her condition.

There was a history of diphtheria and a doubtful history of chorea during childhood. No history suggestive of rheumatic or scarlet fever could be obtained.

She had had dyspnea, palpitation, tachycardia, and peripheral edema of such severity as to necessitate rest in bed for the first time, in May, 1939, about two years before our first visit, although she apparently had not been in good health for a considerable period prior to this incident. From that time until she was seen in March, 1941, the attacks of cardiac failure had recurred frequently, and had become more severe, more frequent, and more prolonged, in spite of all treatment. As the condition progressed, attacks of pain in the chest, fever, cough, and hemoptysis had occurred, and were usually followed by an increase in the degree of heart failure. She said that the heartbeat had been irregular at times.

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Severe abdominal pain, associated with fever, distension, and obstinate constipation, had occurred on several occasions before she came under our care. The pain was described as having been diffuse, although in one instance it became localized in the left flank and left costovertebral region. A moderate leucocytosis was associated with this attack, but no significant urinary abnormalities were present at any time. Enemas and opiates afforded only moderate relief. Roentgenologic studies of the stomach and bowel at a later date revealed no evidence of disease, but a chest roentgenogram at that time was said to have shown cardiac enlargement, with a mitral contour.

On Feb. 21, 1941, during a period of hospitalization, she suddenly became very apprehensive and confused. At that time she gave evidence of difficulty in swallowing and talking, and complained of numbness of the left side of the face and body. The examiner noted muscular weakness of the left side of the face, left arm, and left leg. The information concerning this incident is incomplete, but, within thirty minutes, sensation had begun to return, and no evidence of residual weakness could be detected a few hours later.

The initial examination revealed a very apprehensive and restless white woman, with marked dyspnea and orthopnea. The skin was pale and the mucous membranes were cyanotic. The neck veins were distended and showed forceful pulsations. There was puffiness about the eyes. Râles were heard throughout both lungs, and the percussion note was dull over both lung bases, with diminished breath and voice sounds in those areas. The heart was enlarged to the left. The rhythm was regular and the rate was 120 per minute. The pulmonary second sound was accentuated. No murmurs could be heard. The blood pressure was 132/104. The edge of the liver was felt three finger-breadths below the right costal margin in the midclavicular line. The abdomen was slightly distended, and there was dullness to percussion in the flanks. Pitting edema was present in the ankles and in the dependent portions of the legs and thighs. Urinalysis showed 1 plus albumin, occasional hyaline and granular casts, and occasional pus cells.

She was placed on a restricted fluid and salt intake, and was fully digitalized with a *Digitalis lanata* preparation (Cedilanid, Sandoz), but failed to show much improvement. Large doses of ammonium chloride, followed by a mercurial diuretic, produced a good diuresis, and the edema and respiratory distress diminished considerably. In spite of relatively large doses of digitalis and the use of sedatives throughout the day, the pulse rate remained rapid, ranging from 100 to 130 per minute throughout the greater part of her illness. However, with the use of ammonium chloride and the mercurial diuretic, the respiratory distress was greatly relieved, and only minimal edema was present. At this time a soft systolic murmur was heard at the apex, but soon disappeared. This murmur was occasionally present throughout the course of her illness.

About three weeks after the initial examination, when the heart was well compensated, and shortly after an intravenous injection of the mercurial diuretic, she developed a severe pain in the lower, right side of the thorax. This was followed by a rise in temperature to 101.6° F., cough, and hemoptysis. The dyspnea and cyanosis were increased. Examination of the chest revealed a new area of dullness in the right base, with absent breath sounds and voice sounds in that area. The accentuation of the pulmonary second sound had increased.

This attack was followed very promptly by a return to a state of marked congestive failure. It was regarded as reasonably certain that pulmonary infarction had occurred. Similar incidents occurred quite frequently during the course of her illness, usually when the cardiac failure had diminished. On each occasion the degree of failure increased markedly within a period of twenty-four hours after the onset of the pain.

In July, 1941, she developed pain in the left leg, followed by a marked increase in the edema of that leg, with some pallor of the skin. Since the patient was at home and notification was delayed, she was not seen until about thirty-six hours after the onset. Examination showed tenderness over the great vessels in the groin, and also in the popliteal space. There was no evident temperature difference between the two legs, and the reflexes, muscular movements, and sensations did not appear altered. The edema was so marked that it was questionable whether the dorsalis pedis and posterior tibial pulses were present. The femoral pulse was forceful in the groin, and, although of small volume, the popliteal pulse was present. The edema subsided gradually over a period of two weeks, and there was no evidence of muscular weakness or skin changes. The dorsalis pedis and posterior tibial pulses now were obviously present, but of small volume, and remained so throughout the course. It was thought that she had had thrombophlebitis.

In August, 1941, there was another cerebral attack like that which had occurred on Feb. 22, 1941. The anxiety and confusion were so marked that the patient cooperated very poorly. Swallowing and talking were found to be difficult, but on this occasion there were no paresthesias. Examination revealed no evidence of cranial or other nerve disturbances, nor were any sensory changes detected. Again the incident was very transitory.

About one month later, in September, 1941, an opportunity presented itself to observe her when she was suffering from the abdominal pain already described. The pain, which was very severe, was on this occasion located in both upper quadrants and did not radiate. It was associated with vomiting, marked gaseous distension, and obstinate constipation. The temperature was elevated to 99.4° F. on this occasion. No urinary symptoms could be elicited. The patient cooperated poorly, but the entire upper part of the abdomen seemed tender. The liver was enlarged, but the kidneys and spleen could not be felt, and no other masses could be made out. There was no definite flank or costovertebral tenderness. Urinalysis revealed 1 plus albumin, casts, and occasional leucocytes, but no erythrocytes. Opiates, external heat, and enemas gave only moderate relief, but within a week the pain had disappeared.

On Oct. 29, 1941, the abdominal pain recurred and became so severe that she consented to hospitalization, which she had refused persistently up to this time. The picture on this occasion was similar to that already described. The site of the abdominal pain was variable with each attack, and occasionally varied from day to day during a particular attack. Although never well localized, the pain most frequently occurred in one or both upper quadrants, and on occasion radiated into the chest.

During her hospitalization, repeated attacks of chest and abdominal pain occurred, at which times the temperature was usually elevated, occasionally rising to 102° F. The pulse rate varied from 90 to 130

per minute. At all times there was some evidence of cardiac failure, although ammonium chloride, followed by large doses of mercurial diuretics intravenously, reduced the edema and respiratory embarrassment for short periods. At times during the course there was considerable facial edema, and on two occasions marked anasarca developed. By this time the heart had increased considerably in size and the accentuation of the pulmonic second sound had become much more marked.

An electrocardiogram taken Nov. 3, 1941, revealed normal sinus rhythm, with a rate of 104 per minute. The P-R interval was prolonged to 0.22 second. The QRS interval was 0.09 second. P_2 was of 0.12 second duration, and of greater voltage than QRS_2 . QRS_2 was of low voltage and slurred in all leads. The first ventricular complex consisted of a positive deflection alone in Lead I, and a barely perceptible positive deflection, followed by a negative deflection of 3 mm., in Lead III. QRS_2 was of the M-type, and almost isoelectric. S-T₁ was very slightly depressed, and followed by an erect T₁ of very low voltage. T₂ was isoelectric. S-T₂ was isoelectric, and followed by an inverted T₂ of very low voltage. QRS_3 was diphasic. S-T₃ was elevated 2 mm., with an isoelectric T₃. The negative deflection of QRS_4 was slurred. This record was felt to indicate extensive myocardial damage, with first degree A-V block and probably a myocardial infarct.

A roentgenogram of the chest taken Nov. 7, 1941, showed marked enlargement of the cardiac shadow, without any typical pathologic configuration. There were residual interstitial changes in the upper and lower portions of the right lung which were compatible with resolving infarcts.

Laboratory studies during her hospitalization gave the following results: The blood Kahn reaction was negative. The hemoglobin was 13 Gm., the erythrocyte count, 3,930,000, and the leucocyte count, 10,700; a differential leucocyte count showed 7 per cent stab forms, 74 per cent segmented forms, 18 per cent lymphocytes, and 1 per cent monocytes. A blood smear showed polychromatophilia and occasional nucleated erythrocytes. Urinalysis showed a specific gravity from 1.005 to 1.017, albumin from 0 to 4 plus, no sugar, no acetone, hyaline and granular casts, 1 plus epithelial cells, 2 to 4 leucocytes per high-power field, and no erythrocytes. The blood nonprotein nitrogen was 60 mg./100 c.c. The serum protein was 5.4 per cent.

On Nov. 8, 1941, the edema of the legs increased very rapidly to such an extent that the skin over the entire legs, and especially below the knees, became tense and shiny. At this time she complained of heaviness in the legs and of awkwardness of motion, but there was no pain. On the next day both legs felt numb, and they now appeared pale and slightly cyanotic. The reflexes were found to be present, but sluggish. There was no evidence of sensory disturbance, although the extremities felt cold to the touch and the pulses could not be felt. As the massive edema subsided over a period of several days, the popliteal, posterior tibial, and dorsalis pedis pulses could again be made out bilaterally, although they remained of small volume. Bilateral arterial occlusion of the lower extremities was considered at this time, but was thought to be unlikely because of the return of the pulses and the failure of gangrene to develop.

On Dec. 5, 1941, two nodules about 1 cm. in diameter were noted on the extensor surface of the left forearm. These were slightly movable and slightly tender to the touch. Three days later a similar nodule

appeared in the right cheek, and was attended by slight swelling. In each case the nodules persisted for about five days and then disappeared quite rapidly.

Her condition became progressively worse from this time on. The respiratory embarrassment and edema became more marked, and she required more frequent and larger doses of mercurial diuretic for even moderate relief. Either thoracic or abdominal pain was experienced almost daily at this time. She became increasingly uncooperative, and finally became irrational, and died Jan. 9, 1942.

Summary of Clinical Observations.—A 27-year-old white woman, with a past history of diphtheria and a doubtful history of chorea, suffered from an undiagnosed cardiovascular disease for at least two and a half years, and probably longer. Her illness was marked by dyspnea, orthopnea, cough, and edema. The size of her heart increased during the illness. Occasionally a transient, soft, systolic murmur was heard at the apex, and the accentuation of the pulmonic second sound became more marked. The electrocardiogram showed evidence of extensive myocardial damage. Repeated attacks of thoracic pain, fever, cough, and hemoptysis were considered to be caused by pulmonary infarction. Severe abdominal pain, gaseous distension, and obstinate constipation occurred repeatedly, without urinary symptoms or tenderness over the kidneys. Two cerebral seizures, marked by difficulty in talking and swallowing, confusion, apprehension, anxiety, and transient neurologic disturbances, occurred. The sudden increase in the edema of the lower extremities on two occasions was thought to be caused by peripheral vascular occlusion. The patient ultimately failed to respond to therapy.

AUTOPSY

The body was that of a poorly nourished white woman whose apparent and actual age were approximately the same. The veins of the neck were dilated, an old appendectomy scar was present, and the left ankle was slightly edematous.

The peritoneal cavity contained a small amount of excess fluid, and a few fibrous adhesions were present at the site of the appendectomy. No constriction of the bowel was noted. The left pleural cavity contained about 150 c.c. of clear yellow fluid, and the right cavity, a small amount of the same fluid. Many fibrous adhesions were present in the right pleural cavity. The pericardial cavity contained 200 c.c. of clear fluid.

The heart weighed 460 grams. Irregular patches of scar tissue were present in the myocardium; the largest of these was in the wall of the left ventricle near the apex, and measured 5 mm. in diameter. The valves were soft and thin. On the endocardium of the left ventricle there were many thrombi of all ages. A few of these were seen in the right ventricle also. In the right auricular appendage there was a thrombus 5 cm. in diameter which not only filled the appendage, but also extended out over the tricuspid orifice as a pedunculated mass. The coronary arteries were thin walled, and no evidence of occlusion could be found grossly.

The lungs showed some generalized thickening of the framework, and a large number of infarcts of all ages were seen. The large pulmonary arteries were grossly patent.

The right kidney weighed 100 grams. The capsule was slightly adherent and the surface was congested, with many depressed areas

The cut surface was unremarkable except that many infarcts in various stages of healing were seen. The left kidney was similar to the right.

The aorta was elastic, and its intima was smooth down to about 8 cm. above the bifurcation. Extending from here downward and into the iliac arteries there was a thrombus. Its aortic portion was mural in character; it was situated on the posterior wall of the vessel, and was very pale and firmly attached to the intima. In its iliac portion it occluded the vessels entirely, and varied in structure, i.e., it was red in some portions and somewhat decolorized in others. The veins were entirely patent.

MICROSCOPIC OBSERVATIONS

Heart.—Some hypertrophy of the muscle was present, and there was extensive patchy fibrosis, giving the impression of infarction with healing. The coronary arteries did not appear thickened, and no coronary thrombus could be found. The endocardial thrombus was of various ages in various parts, from a few days in the superficial layers to much longer in the deeper portions, in which there was thorough organization. The structure was typical of a laminated thrombus with organization.

Lungs.—There was chronic passive congestion. The lung framework was greatly thickened. Many infarcts were present; some of these were fairly fresh, but most were in various stages of encapsulation or organization. The arterics were the site of intimal thickening, and a large number were occluded by organized and canalized thrombi. The newly formed vessels in these thrombi were of considerable size in many instances, with muscular walls and a definite elastic tissue component.

Spleen.—Chronic passive congestion, hyperplasia of the lymphoid follicles, and hyaline changes in the smaller arteries were the lesions found here.

The liver was the site of hydropic degeneration and chronic passive congestion. The gastrointestinal tract was the site of slight chronic inflammation in the mucosa.

Kidneys.—Multiple infarcts were present, some of which were fresh, some organizing. Intimal thickening and fibrosis were present in the small and medium-sized arteries, and extreme splitting of the internal elastica was seen in many areas. Organized and canalized thrombi were present in many of these arterics, and the canalizing vessels in some cases had developed fairly thick, partially muscular, walls. A careful search revealed no fresh thrombi.

Aorta.—Typical organized thrombus.

Iliac Arteries.—A fresh, red thrombus was present, with partial organization. The artery wall was approximately normal.

Summary of Pathologic Observations.—The heart was hypertrophic, and, although no coronary sclerosis or thrombosis was found, there were patchy myocardial scars and endocardial thrombi. The small and medium-sized arteries of the lungs and kidneys were the seat of intimal thickening and fibrosis, and in many of these vessels there were organized and canalized thrombi. Multiple infarcts of various ages were present in these organs. A thrombus was present in the lower part of the aorta and common iliac arteries. This was mural in character in the aortic portion, but completely occluded both common iliac arteries. In the aortic portion it was decolorized and or-

ganized, whereas the iliac portion was fairly fresh, with beginning organization. No inflammatory changes were found in the vessel walls or thrombi.

DISCUSSION

This case, although obviously one of generalized vascular disease, defied all attempts at specific clinical or pathologic diagnosis. The pathologic picture corresponded in some respects to that which some investigators have considered as characteristic of thromboangiitis obliterans. Hausner and Allen³ found purely degenerative lesions in the visceral arteries, whereas the peripheral vessels showed the typical inflammatory changes of Buerger's disease. Fatheree and Hines⁴ emphasized the generalized nature of the lesions, and stated that the characteristic inflammatory process occurred but rarely in the visceral arteries, and never without associated degenerative lesions.

Eppinger⁵ regarded the salient features as (1) marked intimal proliferation, (2) extensive thrombosis with canalization, (3) remarkable preservation of the internal elastic membrane, and (4) relatively intact media and adventitia; he merely mentioned, in passing, the lymphocytic infiltration and edema of the media.

In Cabot Case No. 22102,⁶ post-mortem examination revealed extensive, organized, and canalized thrombi in nearly all the medium-sized and small pulmonary arteries. These lesions were similar to those found in the present case, and this condition was considered by the pathologist to be endarteritis obliterans.

In a study of 200 cases, Telford and Stopford⁷ came to the following conclusions: The first change is proliferation of the intima, probably as a result of vasospasm, followed later by thrombosis at the intimal irregularities. The thrombus increases by propagation. Three zones are then seen in a cross section of the artery: (1) the thickened intima, (2) organized thrombus material, and (3) fresh thrombus. When the thrombus extends centrally from the primary thrombus, cross section of the vessel may not show the intimal change. Later there may be fibrosis of the media and adventitia. They do not consider the organization to be of any peculiar type, and emphasize the absence of collections of lymphocytes.

Staemmler⁸ described a case of diffuse disease of the pulmonary arteries, with intimal overgrowth, thrombosis, canalization, and reduplication and splitting of the internal elastica. No actual inflammatory lesions were found, but the author designated the condition as thromboendarteritis obliterans. In his opinion, lymphocytic infiltrations are so common in thrombus organization that no conclusion concerning a primary inflammatory lesion can be drawn therefrom.

Jaeger,⁹ in two articles based on a thorough necropsy study of four cases and the examination of several surgical specimens, stated that the first change is localized fibrinoid necrosis of the intima. This is followed by proliferation of the cells underlying the necrotic portions,

giving rise to the formation of "intimal cushions." Occlusion may follow this process directly or by way of thrombus formation. The reactive granulation tissue is distinguished by abscesslike leucocytic foci, and later by the presence of Langhans-type giant cells and fibroblasts. The distribution may be extremely widespread throughout the vessels of the viscera and extremities. Consequently, thromboangiitis obliterans is classified by Jaeger as a general inflammatory disease of the vascular system.

Buerger,¹⁰ however, objects strenuously to the above theories regarding the pathogenesis of thromboangiitis obliterans. He states that the essential picture is one of vascular inflammation and occlusive thrombosis, and that degenerative lesions are merely coincidental and bear no causal relation to Buerger's disease. He describes two stages: (1) the acute or specific stage, and (2) the healed or organized stage. In the former the changes consist in an acute inflammatory process characterized by infiltration of the vessel coats with polymorphonuclear leucocytes and the occlusion of the lumen by red clot. The specific lesion is a purulent focus in the clot, containing giant cells, endothelioid cells or "angioblasts," and broken-down leucocytes.

Healing takes place, as far as we can ascertain from Buerger's description, in a manner entirely typical for the organization and canalization of any thrombus. He emphasizes the presence of hemosiderin-filled monocytes in the organizing tissue, but in our experience this is not specific, for it may be encountered in any organizing clot. This process leads finally to the complete obliteration of the lumen of the vessel, with recanalization. He also emphasizes the involvement of the veins, and the perivascular fibrosis which binds together the artery, vein, and nerve.

According to Mallory,¹¹ however, other investigators, in studying a large volume of material, have found very little evidence of the acute changes described by Buerger. This may be because of the short duration of the acute process, but this point of view denies the necessity of finding acute changes in order to make a diagnosis of thromboangiitis obliterans.

Mallory also states that, in the opinion of some authors, the changes described by Buerger are not specific, but may be found also in the arteries after trauma, in Raynaud's disease, syphilis, ordinary septic thrombophlebitis, and even frostbite.

In the present case the vascular lesions were found in the abdominal aorta, the iliac arteries, the small and medium-sized pulmonary arteries, and the small and medium-sized arteries of the kidneys. Nowhere was an acute inflammatory lesion found. No unorganized thrombi were found except in the iliac arteries, where organization was just beginning. Intimal thickening was found in both occluded and unoccluded vessels. In some portions, particularly in the kidneys, there were splitting and reduplication of the internal elastica. In some of

the canalized thrombi the organizing vessels were definitely muscular in type, and some had a fairly well-formed elastic membrane.

The veins were not involved as far as could be ascertained, nor was the perivascular fibrosis of Buerger's description found.

The lesions in the heart were puzzling in that the arteries were thin-walled and apparently patent, and yet there were large patches of fibrosis that were fairly typical of healed infarcts. In the organizing ventricular thrombi there were hemosiderin-filled monocytes. No importance was attached to this, however, for pigment may be found in any organizing thrombus.

The clinical picture certainly did not correspond to that usually ascribed to thromboangiitis obliterans as manifested in the peripheral arteries. This disease is unusual in women, and especially so in women under 30 years of age. Telford and Stopford⁷ concluded from their own cases and those collected from the literature that less than 1 per cent of the total number of cases occurred in women.

In the typical case, the presenting symptoms are pain, numbness, and coldness of the lower extremities, and intermittent claudication. The final result of the vascular lesions is usually gangrene. Besides the symptoms caused by arterial changes, phenomena referable to thrombophlebitis may be striking, and are usually described as being of a migratory nature. Buerger presents thrombophlebitis as an essential feature, whereas Telford and Stopford found it in only 10 per cent of their cases.

In the present case, however, no symptoms referable to the peripheral vessels were noted until the visceral manifestations had been established for several years. This fact, in itself, does not necessarily exclude thromboangiitis obliterans; Hausner and Allen^{3, 12} found typical lesions in the visceral arteries preceding those in the peripheral vessels. When our patient finally began to develop the symptoms of peripheral lesions, however, they were not such as would indicate thromboangiitis obliterans. Although she complained of easy fatigue of the legs early in the course of her illness, claudication was never present, nor were there symptoms of migratory thrombophlebitis.

The first indication of involvement of the peripheral vessels appeared about six months before her death. At this time there occurred what seemed to be a major venous occlusion in the left leg. The arterial pulses in this leg disappeared temporarily, but when the edema subsided they reappeared, although they were of small volume.

Again, about two months prior to her death, both legs suddenly became edematous. She complained of heaviness, awkwardness, and numbness of the lower extremities, which now were cold and slightly cyanotic. At this time the arterial pulses disappeared bilaterally, but subsequently reappeared.

The prompt return of the pulses on both of these occasions seemed to rule out the possibility of a major arterial occlusion. The absence

of gangrene bore out this impression, and the finding at autopsy of complete occlusion of both common iliac arteries was totally unexpected.

The nodules on the cheek and left arm, which disappeared before death, remain entirely unexplained. It was considered that these might be related to the vascular system, possibly as a manifestation of periarteritis nodosa, but the vascular lesions which were found in the other organs gave no support to this supposition.

Unfortunately, examination of the brain was not permitted, so that the explanation of the cerebral symptoms must remain entirely a matter of speculation. Hausner and Allen,³ in discussing the cerebral manifestations of thromboangiitis obliterans, suggested that the transient nature of the symptoms implies a vasospasm superimposed on organic lesions. In their experience, hemiplegia was the outstanding symptom, sometimes accompanied by confusion, disorientation, aphasia, loss of memory, and hemianopsia. A review of twenty-three cases from the literature and eleven cases from the Mayo Clinic by the same authors, in 1940,¹² served to confirm their earlier impressions.

The cause of the cardiac disorder was never thoroughly understood clinically. Although there was a doubtful history of chorea and a definite history of diphtheria in childhood, the cardiac abnormalities were not such as to indicate an infectious origin. Examination of the heart revealed little besides progressive enlargement, persistent tachycardia, and an inconstant apical systolic murmur. The electrocardiogram suggested myocardial damage of a type usually associated with coronary disease. On the other hand, the attacks of pain in the chest were rather typically pulmonary in character, and at no time did they suggest coronary disease. The high diastolic pressure was puzzling, in that there was no indication that the systolic pressure had been elevated previous to the onset of heart failure.

The heart muscle was the seat of patchy fibrosis which is usually considered as the end result of sudden or gradual coronary occlusion. Thorough examination of the vessels, however, revealed no thrombi, and the arteries appeared thin walled and widely patent. It was felt, therefore, that the infarcts must have been caused by prolonged spasm of the arteries. Telford and Stopford⁷ stated that the pulses in the affected arteries may come and go; this observation would seem to indicate that spasm may play an important role in the production of the characteristic lesions of thromboangiitis obliterans.

Another possible explanation is suggested by Currens,¹³ who, in a recent paper, based on both his own observations and several reports in the literature, called attention to the electrocardiographic changes in cases of pulmonary embolism; he emphasized especially the finding in some of these cases of myocardial infarcts at autopsy, although no coronary occlusion could be detected. He thought that these infarcts were the result of shock and the consequent lowering of the coronary

arterial pressure, combined with an increase in pulmonary arterial tension and an increased demand on the right side of the heart.

The pulmonary lesions could easily have been caused by embolism, thrombosis, or vasospasm, or, indeed, any combination of these. The endocardial thrombi on the right side formed a ready source for emboli. On the other hand, the changes found even in the unoccluded arteries were of a type often associated with vasospasm, which, in turn, may lead to thrombosis. The decrease in blood supply to the lung brought about in this way, with the added factor of a handicapped heart, was probably the cause of the generalized thickening and fibrosis of the lung framework.

The relation between the state of the cardiac function and the acute pulmonary attacks is another subject for speculation. The symptoms which suggested infarction of the lung frequently occurred during a period of improved cardiac status. Since these attacks occurred frequently after the intravenous administration of a mercurial diuretic, it is possible that the vasospasm that was already present might have been aggravated by the drug, precipitating thrombosis. The chief evidence of cardiac improvement was a decrease in the edema, without any slowing of the pulse rate or change in the heart tones. It was felt, therefore, that the improvement was brought about chiefly by the diuretic, and that an increase in the force of cardiac contraction sufficient to dislodge endocardial thrombi did not take place.

The symptoms which we, in retrospect, have attributed to the infarcts of the kidneys were of little specific diagnostic value. Although renal changes were considered as a cause for these symptoms, there was nothing to point to any specific renal lesion. The pain itself was misleading; its location was in the upper abdominal quadrants, and varied not only in successive attacks, but also during a single attack. At no time was there radiation suggesting renal origin. Associated with the pain were fever, nausea, vomiting, distension, and obstinate constipation. The fact that she had had an appendectomy, followed by peritonitis, introduced another confusing factor, i.e., the possibility of intestinal obstruction caused by adhesions.

The urinary abnormalities were not such as to point to the true cause of the abdominal symptoms. The variable albumin content and the presence of casts were felt to be consistent with the cardiac situation. The absence of hematuria merely added to the negative evidence which allowed the abdominal complaints to go unexplained clinically.

In view of the obvious divergence of opinions on the subject, no attempt has been made to put this case in a definite category in the confused classification of vascular occlusive diseases.

SUMMARY AND CONCLUSIONS

1. A case of generalized arterial disease in a young white woman is presented. The vascular lesions involved chiefly the muscular ar-

teries, and consisted of intimal thickening and fibrosis, splitting of the internal elastica, and thrombosis with organization and canalization.

2. The clinical picture was bizarre, and is conceived to have been the result of vascular changes in the brain, heart, lungs, and kidneys.

3. The classification of the condition is considered with reference to the recent literature concerning thromboangiitis obliterans. The opinions of the various authors with regard to the essential nature of this disease, and also with regard to the criteria for its diagnosis, are at variance. It appears either that this disease varies greatly in its manifestations, or that more than one disease is included under this name.

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ELECTROCARDIOGRAPHIC OBSERVATIONS ON 500 UNSELECTED YOUNG ADULTS AT WORK

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IN A recent study which involved routine electrocardiographic examination of hospital and dispensary patients,¹ we encountered the surprisingly high incidence of 27.2 per cent of abnormal records among 400 subjects who were selected more or less at random from among patients on whom no formal request for an electrocardiogram had been made. Even after eliminating those cases in which some abnormality might have been expected from the history, blood pressure, physical examination, or laboratory data, an entirely unexpected abnormal group, comprising 12.2 per cent of the electrocardiograms, was still left. Because practically half of the abnormal records were found in the younger age group (13 to 35 years old), and because a higher percentage of unexpectedly abnormal tracings occurred consistently in the earlier as compared with the later decades, it was thought important to extend this study to include a large group of relatively young people who were not patients, but were apparently healthy subjects and at work. The results of such an investigation might be of particular current interest to those concerned with the selection of personnel for highly specialized military and industrial needs, like aviation.

It is necessary to emphasize the importance of basing such a study on subjects who are not *patients*, for illnesses other than those of a primarily cardiovascular nature may nevertheless influence the electrocardiogram. Thus, Sprague² has listed forty causes for abnormalities of the RS-T and T portions of the electrocardiogram, only 15 of which are directly concerned with cardiovascular abnormalities, and Leach, Reed, and White,³ in a recent study of low voltage, found that heart disease was of no greater relative importance than extracardiac factors in cases in which this feature was present.

Should study of a large, nonpatient group again disclose an unusually high incidence of electrocardiographic abnormalities, then at least two considerations would arise: (1) that routine electrocardiography is an essential supplement to other methods of examination and is indispensable as a case-finding method in cardiovascular disease, or (2) that our present criteria of what is normal for the electrocardiogram are faulty.

Representing in part an abridgment and in part an extension of a thesis submitted by P. C. V. to Yale University School of Medicine in partial fulfillment of the requirements for the degree of M.D.

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METHODS AND PROCEDURE

Electrocardiograms were obtained on 500 unselected subjects between the ages of 18 and 38 years. There was an equal number of males and females, and the majority were medical students, nurses, or interns; the remainder were hospital technicians or other institutional employees. A relevant history was recorded on each subject, and all had had or were given at least one complete physical examination, including readings of blood pressure, Kahn test on the blood, and one or more roentgenologic examinations of the chest. All of the subjects were seemingly in good health and at work, at the time of the electrocardiographic examination.

Each electrocardiographic record consisted of the three conventional limb leads, as well as the precordial lead CF_4 ,⁴ and the sensitivity of the galvanometer was adjusted to the standard deflection of one centimeter per millivolt. All records were taken with the subjects in the same semi-reclining position to exclude positional variations.

The amplitudes of deflections were measured to the nearest 0.5 mm., and durations to the nearest 0.01 second. When variations were apparent, an average of several measurements was taken.

The criteria by which the electrocardiograms were judged corresponded almost entirely with the standards found in the current *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*, compiled by the Criteria Committee of the New York Heart Association.⁵ These criteria were slightly modified or amplified on the strength of personal experience (indicated by asterisks in the tabulation below) when the authority quoted either made no statement or seemed resting on too little data, as in the case of certain features of Lead CF_4 . Although in practice our criteria are slightly broader in certain minor details than those herein referred to, it was felt that, for the purposes of this study, the criteria of a widely used and official authority should properly serve as the basis for judgment.

RESULTS

Classification of the electrocardiograms as normal, borderline, and abnormal, on the basis of the criteria set forth in Table I, revealed that only 244 of the 500 records, or 48.8 per cent, were indisputably normal, while of the remainder the outspokenly abnormal tracings greatly outnumbered those classified as borderline. These results are summarized in Table II.

Before considering the significance of these observations and attempting to interpret them, it was essential first to investigate the subjects with borderline and abnormal electrocardiograms and to ascertain whether there were cardiovascular abnormalities which might account for some of the deviations from the normal. It was found that only fourteen subjects (2.8 per cent) presented either definite or probable cardiovascular abnormalities. Eight had heart murmurs, six of which were considered organic, and two others were accepted as organic, although the description of the murmurs by another examiner had not been adequate and the subjects were no longer available for re-examination. Four persons had roentgenologic abnormalities in the chest. One

TABLE I

CRITERIA OF NORMAL ELECTROCARDIOGRAPHIC FEATURES ADOPTED IN THIS STUDY*
(Amplitudes: 1 mm. = 0.1 mv.)

LIMB LEADS

P Wave

- Direction: Upward in Leads I and II (except in dextrocardia)
 Amplitude: 0.5 to 2.5 mm. in lead with largest P wave
 Duration: Up to and including 0.10 sec.
 Contour: May be notched if otherwise normal
 †(With respect to the last three, a P wave was judged abnormal only if it exceeded the indicated limits in more than one of the features)

P-R Interval: 0.12 to 0.20 sec.

QRS Complex

- Duration: Not exceeding 0.10 sec. in lead where longest
 Amplitude: Either 5 mm. or more in at least one lead, for sum of over-all dimension in three leads more than 15 mm.
 Contour: Notching or splintering or localized slurring in one lead only, or in more than one lead if confined to apex or base in such other leads
 Q waves in Leads I, II, and III not exceeding 15%, 20% and 25%, respectively, of the largest QRS amplitude in any of the three leads (Criteria do not hold if QRS amplitude exceeds 20 mm., or for Leads II and III in presence of right axis deviation)
 Axis: Net deflection is upward or zero in all three leads (†QRS not longer than 0.10 sec.)

RS-T Junction: Deviation from isoelectric level up to ± 1 mm.

T Wave

- Direction: †Upward in Leads I and II
 Amplitude: At least 1 mm. in Leads I and II

Q-T Duration: The value for K in the formula $Q - T = K \sqrt{\text{cycle length}}$ does not exceed 0.392 in men or 0.440 in women

PRECORDIAL LEAD IV F

P Wave

- Direction: Upward, isoelectric, †diphasic or †inverted up to -0.5 mm.
 Amplitude: †-0.5 mm. to +1.5 mm.

QRS Complex

- Amplitude: †Over-all dimension is 8 mm. or more
 Contour: †Slurring, notching, splintering acceptable
 †Initial positive deflection (R wave) not less than 3 mm.
 Initial negative deflection (Q wave) not more than 3 mm.

RS-T Junction: Deviation from isoelectric level not beyond -0.6 mm. or +2.0 mm.

T Wave

- Direction: Upright
 Amplitude: 0.5 mm. or more

According to criteria adopted by the American Heart Association.

†Personal modifications or additions to criteria.

TABLE II

CLASSIFICATION OF ELECTROCARDIOGRAMS OF 500 UNSELECTED WORKING SUBJECTS

RECORDS	MALES		FEMALES		TOTAL	
Normal	116	46.4%	128	51.2%	244	48.8%
Borderline	33	13.2%	21	8.4%	54	10.8%
Abnormal	101	40.4%	101	40.4%	202	40.4%

man had hypertension and a past history of auricular fibrillation, and one woman had unexplained, periodic edema of the ankles. The abnormal electrocardiographic and clinical observations in these fourteen cases are summarized in Table III.

TABLE III

CLINICAL AND ELECTROCARDIOGRAPHIC DATA IN THE FOURTEEN PATHOLOGIC CASES
ELIMINATED FROM STUDY

ECG NO.	SEX	CLASS #	ECG ABNORMALITIES	CLINICAL ABNORMALITIES
45	M	Ab.	LAD† 1+ (asthenic build) Slurred QRS _{2, 3, 4}	Loud systolic murmur and split sound at apex
40	M	B.	RAD‡ ± Slurred QRS _{2, 3} "K" = 0.406	Deformity from previous empyema and thoracotomy on right
63	M	Ab.	Small QRS ₁ Slurred QRS _{1, 3}	Loud apical systolic murmur. Cardiac displacement (x-ray)
66	M	Ab.	Slurred QRS _{1, 3} ; Broad P "K" = 0.405	Systolic murmur at apex. Scarlet fever and diphtheria in childhood
97	M	B.	LAD 2+ Slurred QRS _{1, 2, 3}	Blood pressure 155/65
236	M	Ab.	LAD 2+; T ₂ inverted Slurred QRS _{2, 3}	Inconstant hypertension. History of scarlet fever and nephritis
247	M	B.	Slurred QRS _{1, 3} T waves all low	Blood pressure 170/100. Paroxysmal auricular fibrillation
312	F	Ab.	Low QRS ₁ with absent R ₁	Periodic edema, ? etiology
351	F	N.	LAD 1+	Signs of mitral stenosis
353	F	Ab.	T ₂ absent	Harsh apical systolic murmur. Auricular enlargement (x-ray)
360	F	Ab.	Small QRS ₁ (R ₁ = 1 mm.) QRS slurred in all leads	Apical systolic murmur. Patient not available for recheck
415	F	Ab.	Small QRS ₁ (R ₁ = 1 mm.) Low voltage	Left auricular enlargement (x-ray)
447	F	Ab.	QRS slurred in all leads T ₂ absent; S-T ₂ = -2 mm.	"Systolic murmur" (patient not available for recheck)
452	F	Ab.	T ₂ absent, S-T ₂ = -1.5 mm.	Blood pressure 140/90

*Ab, Abnormal; B, borderline; N, normal.

†LAD, Left axis deviation.

‡RAD, Right axis deviation.

Elimination of the fourteen abnormal cases from the study still left 242 (49.8 per cent) of the records in the abnormal and borderline groups, of which the great majority were definitely abnormal on the basis of the established criteria. The classification of these records is given in Table IV.

Inspection of Table V reveals that although the abnormal and borderline features consisted predominantly of those in which the personal

element of judgment is necessarily involved (as in slurring of the QRS complex), and others which are not always considered in clinical practice (as with abnormally long Q-T interval), it is to be noted that significant contributions are represented also by features that command everyday attention (such as abnormalities of the T wave, low QRS voltage, and considerable axis shift).

TABLE IV

CLASSIFICATION OF ELECTROCARDIOGRAMS OF 486 APPARENTLY NORMAL SUBJECTS

RECORDS	MALES		FEMALES		TOTAL	
Normal	117	48.2%	127	52.2%	244	50.2%
Borderline	28	11.5%	21	8.6%	49	10.1%
Abnormal	98	40.3%	95	39.2%	193	39.7%

TABLE V

ABNORMAL AND BORDERLINE ELECTROCARDIOGRAPHIC FEATURES ENCOUNTERED IN 500 YOUNG ADULTS AT WORK

ABNORMAL FEATURES	ABNORMAL		BORDERLINE		TOTAL	
	NO.	%	NO.	%	NO.	%
<i>Limb Leads</i>						
P inverted in two leads	1	0.2			1	0.2
P duration exceeding 0.11 sec.	1	0.2			1	0.2
P-R duration of 0.22 sec. or more	4	0.8			4	0.8
QRS duration of 0.12 sec. or more	2	0.4			2	0.4
Low voltage	9	1.8			9	1.8
Slurred in two or three leads	28	5.6	98	19.6	126	25.2
Abnormally deep Q ₁	2	0.4			2	0.4
Abnormally deep Q ₃	6	1.2			6	1.2
RS-T depressed more than 1 mm.	3	0.6			3	0.6
elevated more than 1 mm.	3	0.6			3	0.6
T abnormal direction or amplitude	21	4.2	1	0.2	22	4.4
Axis shifts more than slight	5	1.0	5	1.0	10	2.0
Frequent ectopic beats			1	0.2	1	0.2
Abnormally long Q-T	85	17.0			85	17.0
<i>Chest Lead IVF</i>						
P inverted 1.0 mm. or more			39	7.0	35	7.0
Q abnormally large	2	0.4			2	0.4
QRS low voltage	78	15.6	2	0.4	80	16.0
R abnormally small or absent	2	0.4	2	0.4	4	0.8
T abnormal direction or amplitude	19	3.8			19	3.8

It is acknowledged that even the most careful selection of normal subjects is not an infallible procedure, but it is unthinkable that practically half of such a large group would have undiscovered causes for electrocardiographic abnormalities. Moreover, this fact recalls our previous disclosure¹ of abnormal electrocardiograms in an unexpectedly high percentage of hospital and dispensary patients who were not afflicted with cardiovascular disease.*

*The higher incidence of abnormalities recorded in the present study, as compared with the earlier one referred to, is probably due largely to two factors: (1) a difference in technique, for many of the electrocardiograms in the previous investigation were visualized on a fluoroscopic lag-screen attachment to the electrocardiograph, and some abnormalities might have escaped detection, and (2) no attention was paid in the previous study to Q-T duration, which directly contributed twenty-nine records to the abnormal group.

The conclusion seems forced that the current criteria of normality for the electrocardiogram are faulty in being too narrow, and, on the basis of such criteria, we agree with the recent observations of Wood, Wolferth, and Miller⁶ that electrocardiographic surveys would be misleading if applied as a screening technique in mass examinations of candidates for specialized military and industrial posts, or in examinations of life insurance applicants.

SUMMARY AND CONCLUSIONS

An electrocardiographic study of 500 apparently healthy, young, working adults disclosed that half of the records fell outside the range of normal on the basis of authoritative electrocardiographic criteria of normality in current general use. The implication is that electrocardiographic surveys will be misleading unless criteria of what is normal are revised and broadened.

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ON CERTAIN APPLICATIONS OF MODERN ELECTROCARDIOGRAPHIC THEORY TO THE INTERPRETATION OF ELECTROCARDIOGRAMS WHICH INDICATE MYOCARDIAL DISEASE

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INTRODUCTORY REMARKS

FOR nearly thirty years the medical profession has been interested in the problem of interpretation of the electrical effects of the heartbeat. The property of living cells which is characterized by their ability to produce detectable electrical effects is called excitability. This is a property enjoyed not only by cardiac muscle, but by nerve and striated muscle as well. A striking similarity exists between the electrical effects of excitability in these different kinds of tissues and in other cells of both the plant and animal kingdoms. The fields are new and in them much awaits to be done.

An understanding of the electrical effects produced by the heartbeat is not easily obtained by the physician. The chief difficulty lies in the fact that men who are trained primarily as physicians must herein deal with the relatively foreign agent, electricity. Physicists have found that electricity is most conveniently described in mathematical language, but mathematics is a tool for which most physicians entertain a strong aversion. Consequently, a treatise of this kind, although it demands an occasional mathematical expression for accuracy's sake, is best supported by word pictures as well. The more advanced mathematical expressions, which are not essential for a useful grasp of the subject, are relegated to footnotes. Expressions which are retained in the main body of the script are of a simple kind and lend themselves to direct geometric visualization. It is all too obvious that only those physicians who have undertaken the laborious task of becoming familiar with the relevant theoretical physics of electricity are in a position to formulate sound electrocardiographic theory. Between past and present investigators, who are thus qualified, there have been and are no important differences of opinion regarding the interpretations placed upon their own investigative observations or those of others.

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SECTION I

ON VECTORS AND ELECTRICITY

One may choose any number and give it a sense, positive or negative. The number is now a scalar quantity with two properties, magnitude and sense. Certain quantities are met with in dealing with electricity which possess direction as well as magnitude and sense. These are referred to as vector quantities. They are defined completely by the directed line or vector. The direction of the line, indicated by the arrowhead, is the direction of the vector. The length of the line denotes the magnitude of the vector. The sense of the vector is indicated by the plus (usually omitted) or minus sign. The point in space from which the directed line begins is called the origin of the vector. The point in space at which the directed line ends is called the terminus of the vector. In script, vectors or the quantities which they represent are denoted by boldface or clarendon type or by an arrowhead over the letter.

The present subject demands familiarity with three manipulations of vectors, i.e., the translation of a vector, the sum of two or more vectors, and the projection of a vector.

Any two vectors are considered equal if they are identical in direction, magnitude, and sense. The translation of a vector is performed by moving the vector about in space from one position to another without changing its direction, magnitude, or sense. A vector is obviously equal to each of its translations. When the sense of a vector is altered from negative to positive, or vice versa, its direction in space is reversed.

In forming the sum of two vectors \hat{A} and \hat{B} , a translation of the vectors to a common origin is first carried out. The parallelogram of which \hat{A} and \hat{B} form two sides is then completed. Finally, a directed diagonal of the parallelogram is drawn, commencing at the common origin of the two vectors. The directed diagonal \hat{C} is a new vector representing the sum or resultant of the vectors \hat{A} and \hat{B} . Thus, the meaning of the relation,

$$(1-1) \dots \quad \hat{A} + \hat{B} = \hat{B} + \hat{A} = \hat{C},$$

is made clear. An angle formed by two vectors, such as that formed by \hat{A} and \hat{B} before or after translation, may be denoted by the symbol (\hat{A}, \hat{B}) . The occasion often arises in which it is desired to refer to the magnitude of a vector rather than to the vector itself. For this purpose the notation usually adopted is that which uses the corresponding capital letter uncovered by the arrowhead. Thus A is the magnitude of the vector \hat{A} . Moreover, if the magnitude of the vector \hat{A} is 10 units, we have the following identities, $\hat{A} = A\hat{a} = 10\hat{a}$, and $A = 10$. The first three equalities are vector expressions, whereas the last two are scalars. A vector quantity is never equated to a scalar quantity.

In order to project a vector upon a line or plane, two normals are dropped from the extremities of the vector upon the line or plane. The

directed line connecting the feet of the normals is a new vector, the projection of the former upon the line or plane. One normal always connects the origins of the two vectors and the other connects their termini. Let \hat{A} be a vector and let \hat{B} represent the projection of \hat{A} , then¹

$$(1-2) \dots \hat{B} = A \cos(\hat{A}, \hat{B}) \hat{b},$$

where \hat{b} is a unit vector in the direction of \hat{B} , and the quantity $\cos(\hat{A}, \hat{B})$ is a scalar representing the magnitude of \hat{B} in terms of the magnitude of \hat{A} and the angle made by the vectors \hat{A} and \hat{B} . The validity of eqn(1-2) is made obvious in the following way. Let \hat{B} (Fig. 1, a) be the projection of \hat{A} upon the line op . In the right triangle, $\cos(\hat{A}, \hat{B})$ is by definition B/A . Consequently,

$$B = A \cos(\hat{A}, \hat{B})$$

and

$$B\hat{b} = A \cos(\hat{A}, \hat{B})\hat{b}$$

so that

$$\hat{B} = A \cos(\hat{A}, \hat{B})\hat{b}$$

which states that the projection of a vector (upon a line or plane) is itself a vector with a magnitude equal to the product of the magnitude of the projected vector by the cosine of the angle made by it and its projection, and having the direction of the projection.

We may regard electricity as consisting of minute particles, called electrons, which have mass and possess a negative charge. The nature of the electricity with which we are at present concerned is the so-called ionic electron charge. When molecules of certain substances are in solution they dissociate to a variable extent into particles of one or more elements, called ions, which possess either a positive or negative charge. The positively charged ion is known as the cation, and the negatively charged ion is known as the anion. Between any two ions of unlike charge, or between any two groups of ions of unlike charge, there exists a force of attraction. The force acts in accordance with a fundamental law of electricity which states that unlike charges attract, and like charges repel, each other.

The ability of an electric source to produce a flow of current in the region surrounding the source is another electrical fundamental. Every point in the region surrounding an electric source at which the flow of current is present constitutes the electric field due to the source. The medium in which the source is located and throughout which the field extends is known as the *conductor*. When a positive source distribution is responsible for an electric field, the source distribution is referred to as the source of the field. When a negative source distribution is responsible for a field, the former is referred to as the sink of the field.

It is clear that, if the bio-electric process under consideration is in the nature of an electrolytic dissociation, the field will be produced by both sources (+ ionic charges) and sinks (- ionic charges). The particular spacial arrangement of the sources and sinks is called the source-sink distribution. If the medium which surrounds the distribution extends in all directions, it constitutes a volume conductor. If each part of the volume conductor is composed of a like substance, or substances which conduct alike, the medium is said to be homogeneous.

In man we are dealing with a source-sink distribution within the heart muscle which generates an electric field extending outward in all directions to the body surface. Although the body trunk is composed of different kinds of tissues, and is not, therefore, homogeneous, the concentration of electrolytes in the various regions is sufficiently similar to permit treating the body as a homogeneous volume conductor.² Inasmuch as the body is surrounded by air, a nonconducting medium, the electric field produced by the heartbeat does not extend beyond the body surface.

The distribution of current flow throughout the field in a volume conductor of this kind depends upon the particular distribution and strength of the source-sink combination, upon the extent and shape of the conductor, and upon the particular composition of the conductor.

Perhaps the most simple example is the field produced by a point source in a homogeneous volume conductor of infinite extent. The direction of the flow is radially outward from the source in all directions along straight lines extending from the source to infinity. Let us consider any point p in the field. The electrical force at p is a vector quantity with the properties of direction, magnitude, and sense, and is referred to as the electrical intensity at p . The direction of the electrical intensity along a line (of force) in the field determines the direction of the current flow. The line of force is thus referred to as the line of flow. If the vector \mathbf{E} denotes the electrical intensity at p , then, by the usual notation, the magnitude of the intensity is E . If e denotes the strength of the point source, and r denotes the distance of p from the source, it is known that

$$(1-3) \dots \quad E = \frac{e}{r^2},$$

which states that the magnitude of the electrical intensity at any point in the field is directly proportional to the strength of the source and inversely proportional to the square of the distance of the field point from the source. Moreover, if \hat{e} is a unit vector in the direction of \mathbf{E} , we may write

$$(1-3) \dots \quad \mathbf{E} = \frac{e}{r^2} \hat{e}.$$

Another important property of the electrical field is the so-called electrical potential. Let us imagine that we have access to a minute positive "test particle" of negligible mass which we can carry about and place at any arbitrary field point. The charge on the particle is regarded as too small to have any effect on the field, that is, too small to be regarded as part of the source of the field. If the particle is carried to any field point p , it will be acted upon by the electrical intensity at p .

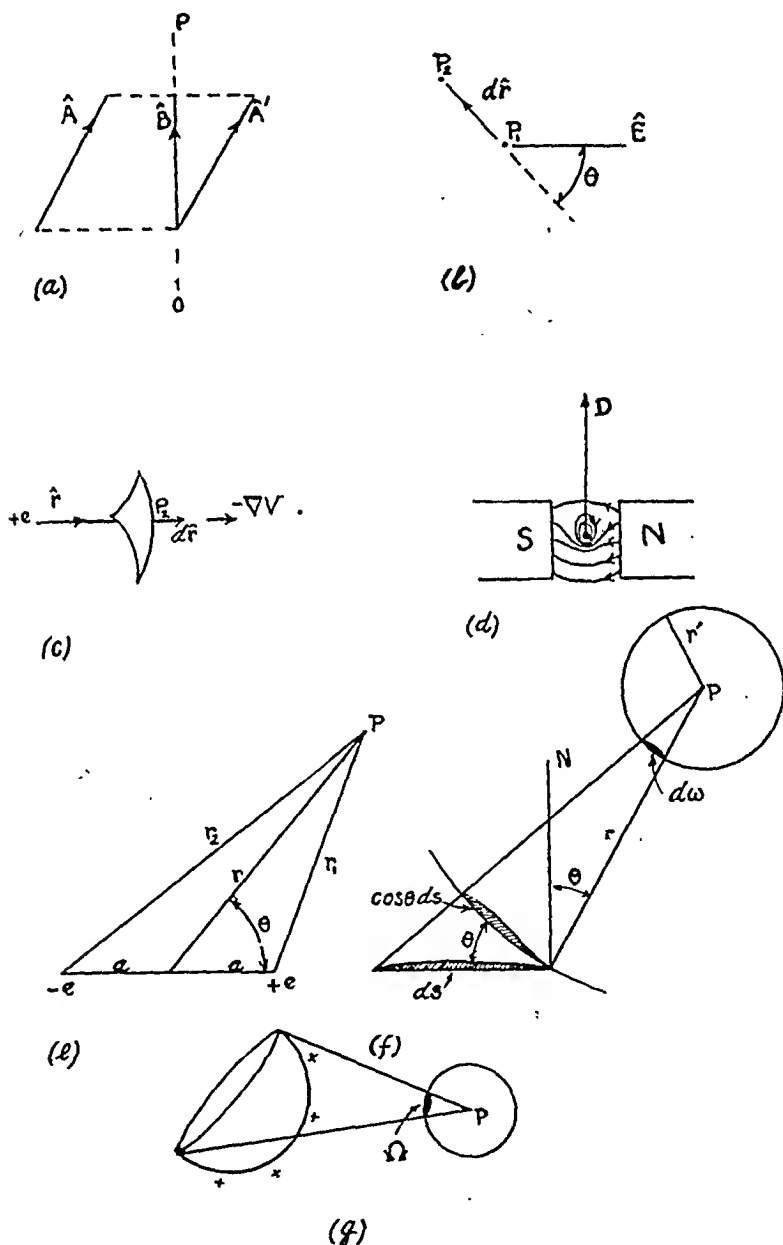


Fig. 1.—(a) The projection of a vector. (b) and (c) Geometry for the calculation of the potential. (d) Galvanometer string movement. D indicates the direction of displacement when the current flows into the paper. (e) Doublet potential. (f) Geometry of the solid angle. (g) Visualization of the solid angle subtended by the closed boundary of an arbitrary double-layer surface at the field point p . See text.

Inasmuch as the sense of the source and the sense of the particle are both positive, the action is one of repulsion. If the test particle is released at p , the force of repulsion will carry the particle in a direction away from the source to some point outside the field, that is, to infinity. If we start from infinity, and carry the particle to any field point p , work is done in overcoming the force of repulsion. The amount of work done may be regarded as stored up on the particle in the form of energy of position which may be reclaimed in the form of energy of motion when the particle is released and returns to infinity. While the particle is at p , its energy of position is equivalent to the so-called electrical potential at p . Consequently, we may define the electrical potential at any point in the field as numerically equal to the work done in carrying a test particle from outside of the field to the point in question. When the field is due to a point sink, the action on the particle is one of attraction, and the work done is then regarded as a negative quantity. The electrical potential is thus a scalar quantity. Its value in our present example may readily be found.*

The resistance of a conductor may be defined as the property which enables it to offer a measure of difficulty to the flow of electricity through it. The amount of resistance offered by a given conductor depends,

*Let the potential V_1 at the field point p_1 (Fig. 1, b) be less than the potential V_2 at the field point p_2 . Let $d\mathbf{r}$ denote the element of path in the direction of the displacement p_1p_2 . The increase of potential dV encountered in traversing the displacement in the direction of $d\mathbf{r}$ is numerically equal to the amount of work done in carrying a test particle from p_1 to p_2 against the force of repulsion, or the electric intensity \mathbf{E} . Let θ denote the angle $(\mathbf{E}, d\mathbf{r})$. Then $E \cos\theta$ is the magnitude of the intensity encountered in traversing the displacement $d\mathbf{r}$. The product of this force by the distance dr is equivalent to the amount of work done in carrying the test particle over the path p_1p_2 . That is,

$$dV = E \cos\theta \, dr = \mathbf{E} \cdot d\mathbf{r}$$

But the electric intensity \mathbf{E} is equal to the negative gradient of scalar potential $-\nabla V$. Also, at any distance r from e , $\mathbf{E} = \frac{e}{r^3} \mathbf{r}$ (by Coulomb's law). Thus we have (see Fig. 1, c)

$$dV = -\nabla V \cdot d\mathbf{r} = -\frac{e}{r^3} \mathbf{r} \cdot d\mathbf{r} = -\frac{e \, dr}{r^2}$$

Let us denote by R the distance from e to the field point p_2 . Then, the potential at p_2 is equivalent to the amount of work done in carrying the test particle from infinity to p_2 by any path. That is

$$V = -e \int_{\infty}^R \frac{1}{r^2} \, dr$$

When computing the integration we may use the standard formula $\int X^n \, dx = X^{n+1}/n+1$, where $X = r$, and $n = -2$. Thus

$$-e \int_{\infty}^R \frac{1}{r^2} \, dr = -e \left(-\frac{1}{r} \right)_{\infty}^R = -e \left[\left(-\frac{1}{R} \right) - \lim_{r \rightarrow \infty} \left(-\frac{1}{r} \right) \right],$$

where the limit approached by $-\frac{1}{r}$ as $r \rightarrow \infty$ is zero. Consequently,³

$$(1-4) \dots \quad V = \frac{e}{R}$$

This expression indicates that the potential is directly proportional to the strength of the source and inversely proportional to the distance from the source to the field point at which the potential is measured.

among other things, upon the particular kind of material of which the conductor is composed. The specific resistance of a conductor may be defined as the amount of resistance offered by a cubic centimeter of the substance to the flow of current through it. If we denote by k the value of the specific resistance, its reciprocal $1/k$ is known as the specific conductivity of the conductor. The value of the potential has been found to vary inversely with k . In our example, the potential V varies directly with the strength of the source and inversely with the distance of the field point from the source. Hence,

$$(1-5) \dots \quad V = \frac{1}{k} \frac{e}{r}.$$

An electrical field may conveniently be regarded as made up of lines of flow and equipotential surfaces. A line of flow is defined as a line drawn in an electrical field in such a way that its direction at every point has the direction of the electrical intensity at that point. All lines of flow begin on sources and terminate on sinks. In our example of the point source in an infinite homogeneous volume conductor, the lines of flow commence at the source and extend outward in all directions along straight courses to terminate upon a sink "scattered at infinity."

Thus far, the more important properties of an electrical field produced by a most simple source distribution have been briefly discussed. It is observed that the relations connecting certain of these properties are likewise quite simple. Since the electrical field depends upon all the sources and all the sinks, as well as upon the size and shape of the conductor, the relations connecting the properties of the field will, in general, become more complex when the source-sink distribution is more elaborate or when the extent of the conductor is finite and of asymmetrical form.

Actually, the value of the potential at a field point cannot be measured conveniently. The instrument used is a galvanometer which must be connected with the field at two points by lead wires from its two terminals. An electric current then flows through the galvanometer from the field point at which the value of the potential is great, and enters the conductor at the field point at which the value of the potential is relatively small. The strength of the current flowing through the galvanometer is proportional to the difference of the values of the potential at the field points under investigation. For this reason the galvanometer is said to measure the potential difference (P.D.) across the two field points in question. The P.D. is commonly referred to as the measured electromotive force (E.M.F.). If V_1 and V_2 denote the great and small values, respectively, of the potential at the field points, we have

$$(1-6) \dots \quad \text{E.M.F.} = V_1 - V_2.$$

The current, in completing the body-galvanometer circuit, flows from one field point to the other through the galvanometer and back

to the point of high potential through the conductor of the field. The measured E.M.F. may, therefore, be looked upon as a vector quantity with a magnitude which is determined numerically by the value of the P.D., a direction away from the point of low toward the point of high potential, and always a positive sense.

The instrument in general use is the string galvanometer of the Einthoven type. Its essential parts consist of a horseshoe-shaped field magnet with its north pole N and south pole S (Fig. 1, *d*) opposing each other across a small gap. From the north pole N to the south pole S are straight parallel lines of magnetic force which comprise the effective magnetic field. Piercing the magnetic field at right angles to the lines of magnetic force is a delicate fiber (a quartz thread coated with gold or silver) which conducts the current that is led off the electrical field under investigation. When this current flows through the galvanometer fiber, it creates an electromagnetic field about the fiber. The character of this field may be determined by the right hand rule, i.e., imagine the fiber grasped with the right hand in such a way that the thumb rests along the fiber in the direction of the current flow; the direction of the circular lines of electromagnetic force is then given by the direction of the fingers grasping the fiber.

Let us consider the gap where the field produced by the current in the fiber is impressed upon the field of the magnet. On one side of the fiber the directions of force of both fields are alike. On the other side of the fiber their directions are unlike. Consequently, the total strength of the two fields is greater on the former than on the latter side, and the fiber will move away from the strong, toward the weak, field. The displacement of the fiber is proportional to the strength of the current flowing within it, and the direction of the displacement is according to the direction of the current flow. If the index finger of the right hand is held straight, and this finger and the thumb and middle finger are held in mutually perpendicular directions, and if the hand is now turned in such a way as to make the index finger point in the direction of the current flow within the fiber while the middle finger points in the direction of the lines of magnetic force of the field magnet, the direction of the thumb indicates the direction of the displacement of the fiber (Fig. 1, *d*). A source of light is used to cast the shadow of a small segment of the fiber upon a moving sensitive film. The motion of the film, together with the motion of the fiber, serves to graph the completed record. The motion of the film is at right angles to the line of displacement of the fiber. Consequently, time is the independent, and voltage the dependent, variable. Whether a given electrocardiographic deflection is positive (above the base line of the curve) or negative (below the base line of the curve) will depend simply upon the direction of the current flow within the fiber or upon the relative values of the potential at the two field points under investigation.

SECTION II

ON THE ELECTRICAL EFFECTS PRODUCED BY THE
CARDIAC MUSCLE CELL

Inasmuch as the electrical effects produced by a mass of cardiac muscle represent the sum of the effects produced by the muscle cells individually, a discussion of the latter, more simple, mechanism serves doubly well for introduction.

It is convenient to assume that the cardiac muscle cell is of cylindrical form. Actually its form is, for our present purpose, immaterial. Presumably a protoplasmic layer bounds the cytoplasm and acts during certain periods as a semipermeable membrane with respect to the electrolytic content of the cytoplasm. A membrane of this kind permits cations to diffuse through it while it holds the anions back. Diffusion continues until the electrostatic force exerted between the ions on the two sides of the membrane is equal to the force of diffusion or osmotic pressure. Thus a state of equilibrium is reached, and the cell is said to be in the resting electrical state. The positive charge on the cations outside the membrane and the negative charge on the anions inside the membrane serve as the source and sink distribution for the production of an electrical field. The layer of sources on the outer surface, considered together with the layer of sinks on the inner surface, is spoken of collectively as a double-layer. The magnitude of the source per unit of membrane surface is equal to the magnitude of sink per unit of membrane surface. The magnitude or strength of the source-sink distribution per unit of membrane surface is the same for all parts of the membrane, and the cell is said to be polarized. The term "intensity of polarization" refers to the strength or electrical moment of double-layer per unit of membrane.²

The relation* $V = \phi \Omega$ is very useful in electrocardiographic analysis,

*It is desirable to know the nature of the electrical field produced by the resting cell. The double-layer has the configuration of a closed cylindrical surface, and the cell is regarded as lying within a homogeneous conducting medium of large extent. The double-layer is regarded as composed of point sources and point sinks. Neglecting the nature of the substance of which the conductor is composed, the potential V_1 at any point p due to a point source is given by eqn(1-4); that is,

$$(2-1) \dots V_1 = \frac{e}{r_1}$$

and in a similar manner the potential V_2 at p due to a point sink is given by the relation

$$(2-2) \dots V_2 = -\frac{e}{r_2}$$

where e and $-e$ of these relations represent the strengths of the source and sink, respectively, and where r_1 and r_2 are the respective distances from the source and from the sink to the field point p . The potential V at p due to both source and sink is given by the sum of the right-hand members of eqns(2-1) and (2-2); that is

$$(2-3) \dots V = e\left(\frac{1}{r_1} - \frac{1}{r_2}\right)$$

Upon writing the fractions with a common denominator and multiplying the numerator and the denominator by $r_2 + r_1$, we have

$$(2-4) \dots V = e\left(\frac{r_2^2 - r_1^2}{r_1 r_2 [r_2 + r_1]}\right)$$

(Footnote continued on next page.)

and its application is reasonably simple. V denotes the potential at a point in the field produced by an arbitrary area of double-layer. The numerical value of the constant ϕ is not known at this time, and is, in fact, immaterial for our present purpose. Actually, ϕ has the dimensions of an electromotive force across the double-layer, and its value depends upon a number of factors.² On the other hand, the solid angle is shown in Fig. 1, *g*, and appears subtended at an arbitrary field point p by the boundary of an arbitrary section of double-layer. The solid angle Ω is defined and measured by the area of spherical surface cut off the unit sphere (inscribed about p) by the cone formed by drawing lines from p to every point upon the boundary of the double-layer. The sense of the solid angle is positive or negative, according to whether an observer stationed at p , and looking through the base of the cone, views the positive or negative charge on the double-layer. During this operation the membrane is conveniently regarded as opaque. In practical application, it is not necessary to calculate the area cut off the unit

Let us consider Fig. 1, *c*. The cosine law states that, for any triangle, the square of the side opposite an angle is equal to the sum of the squares of the other two sides, less twice the product of these sides by the cosine of their included angle. Moreover, the supplementary obtuse angle is $180^\circ - \theta$; thus, $\cos(180^\circ - \theta) = -\cos\theta$. We may now express r_2 and r_1 in terms of r , a , and θ . We get $r_2^2 = r^2 + a^2 + 2ar \cos\theta$, and $r_1^2 = r^2 + a^2 - 2ar \cos\theta$. Consequently, $r_2^2 - r_1^2 = 4ar \cos\theta$. Inserting the right-hand member of the last relation for its identity in eqn(2-4), we have

$$(2-5) \dots \quad V = c \frac{4ar \cos\theta}{r_1 r_2 (r_2 + r_1)}$$

Inasmuch as the source and sink lie very close together, a is very small in comparison with r , so that r_1 and r_2 become nearly equal to r . Here, the source-sink distribution is known as a doublet, and the denominator of the fraction in eqn(2-5) is equivalent to $2r^2$. Thus²

$$(2-6) \dots \quad V = 2ac \frac{\cos\theta}{r^2}$$

If we denote the constant $2ac$ by ϕ , the latter is known as the moment of the doublet, and the right-hand member of eqn(2-6) becomes $\phi \cos\theta/r^2$.

The double-layer under consideration may be regarded as composed of a sheet of doublets arranged to form an arbitrary curved surface S , in which the axis of each doublet is in the direction of the outward drawn normal to S . The elementary potential dV at p , due to an element ds of surface S , may be written down at once from eqn(2-6). Thus,

$$(2-7) \dots \quad dV = \phi \frac{\cos\theta}{r^2} ds,$$

where r is the distance from ds to p ; N (Fig. 1, *f*) is the outward drawn normal to S ; θ is the angle made by N and r ; and ϕ , a constant, is the electrical moment of the double-layer. Let a sphere of radius r be inscribed about p . The angle made by ds and the small portion of the spherical surface adjacent to ds is equivalent to θ , for the corresponding sides of these angles are mutually perpendicular. Inasmuch as ds is an infinitesimal, $\cos\theta ds$ is merely the projection of ds upon the spherical surface of radius r .

Let a spherical surface of radius $r' = \text{unity}$ be inscribed about p , and let lines be drawn from p to every point upon the boundary of ds . The cone thus formed cuts an area of spherical surface $d\omega$ from the unit sphere, and an area of spherical surface $\cos\theta ds$ from the sphere of radius r . Moreover, $d\omega$ is defined as the elementary solid angle subtended at p by the boundary of ds . Obviously, $\cos\theta ds/r^2 = d\omega/r'^2$, for both $\cos\theta ds$ and $d\omega$ are areas of spherical surface cut off from concentric spheres by the same cone. In this last equality, however, r'^2 is simply unity. Hence, $\cos\theta ds/r^2 = d\omega$. Consequently, $dV = \phi d\omega$, which, on integration, becomes²

$$(2-8) \dots \quad V = \phi \int_S d\omega = \phi\Omega$$

The surface integral expresses the sum of all the elementary solid angles subtended by the surface elements of S at p . Hence, Ω is the solid angle defined and measured by the area cut from the unit sphere by the cone formed by drawing lines from p to every point upon the boundary of the double-layer S .

sphere by the cone. On the contrary, it is sufficient to simply visualize geometrically the magnitude and sense of the solid angle. Inspection of Fig. 1, *g* shows at once that the magnitude of the solid angle is entirely independent of the configuration of surface of double-layer.

It will be instructive to examine farther the potential of the field produced by the arbitrary hemispherical distribution (Fig. 1, *g*) of double-layer. If the field point lies anywhere in the plane circumscribed by the boundary of the double-layer, the cone degenerates into this plane surface and cuts off half of the surface of the unit sphere inscribed about the new field point in question. The whole surface of the unit sphere is 4π . Hence, the magnitude of Ω is 2π for all points in the plane specified. If the field point is anywhere in the extension of this plane beyond the boundary of the double-layer, the cone again degenerates into a plane surface, but cuts no area off the unit sphere. Consequently, Ω is zero and the potential at any such point is zero. Finally, if the field point is anywhere upon the axis normal to, and intersecting, the center of the plane circumscribed by the boundary of the double-layer, Ω is numerically maximum with respect to its value at all other points not on the axis at a like distance from the intersection.

Let us now choose any field point p_1 inside the closed surface of double-layer of the resting cylindrical cell. Let any plane whatever be passed through p_1 , thus dividing the closed surface of double-layer into two parts. The magnitude of Ω at p_1 , due to one part of the double-layer, is 2π and negative. The magnitude of Ω at p_1 , due to the other part of double-layer, is likewise 2π and negative. Hence the potential at any point p_1 , inside the resting cells, is $-4\pi\phi$, and this value holds for a resting cell of any shape whatever.

Let us denote by p_2 any field point outside the double-layer of the resting cell. We may let any plane whatever pass through the closed surface of double-layer, thus dividing it into two parts. The solid angle subtended at p_2 by the boundary of one part of the double-layer is equal in magnitude and opposite in sign to the solid angle subtended at p_2 by the boundary of the other part of the double-layer. Hence the potential at any point outside the closed surface of double-layer is zero. Moreover, the potential difference encountered while traversing the double-layer is $4\pi\phi$.

The foregoing relations are based on the assumption that the extent of the conductor is infinite. They must hold for practical purposes, however, in defining the potential of the field near by a double-layer situated at the center of an extensive homogeneous volume conductor.

When the resting cell is stimulated, a change in the characteristics of the membrane takes place at the point of stimulation and spreads with a uniform velocity in all directions throughout successive elements of membrane. The first event in the change of membrane characteristics is such that the polarity of the source-sink distribution is reversed.⁴ The

term accession has become attached to the initial reversal of polarity. The apparent movement of the reversal process along successive elements of membrane is referred to as the accession wave. When the polarity of the double-layer has become reversed at all points, the cell is said to be in the active or excited electrical state. In a relatively brief time after accession, a second wavelike change of membrane characteristics takes

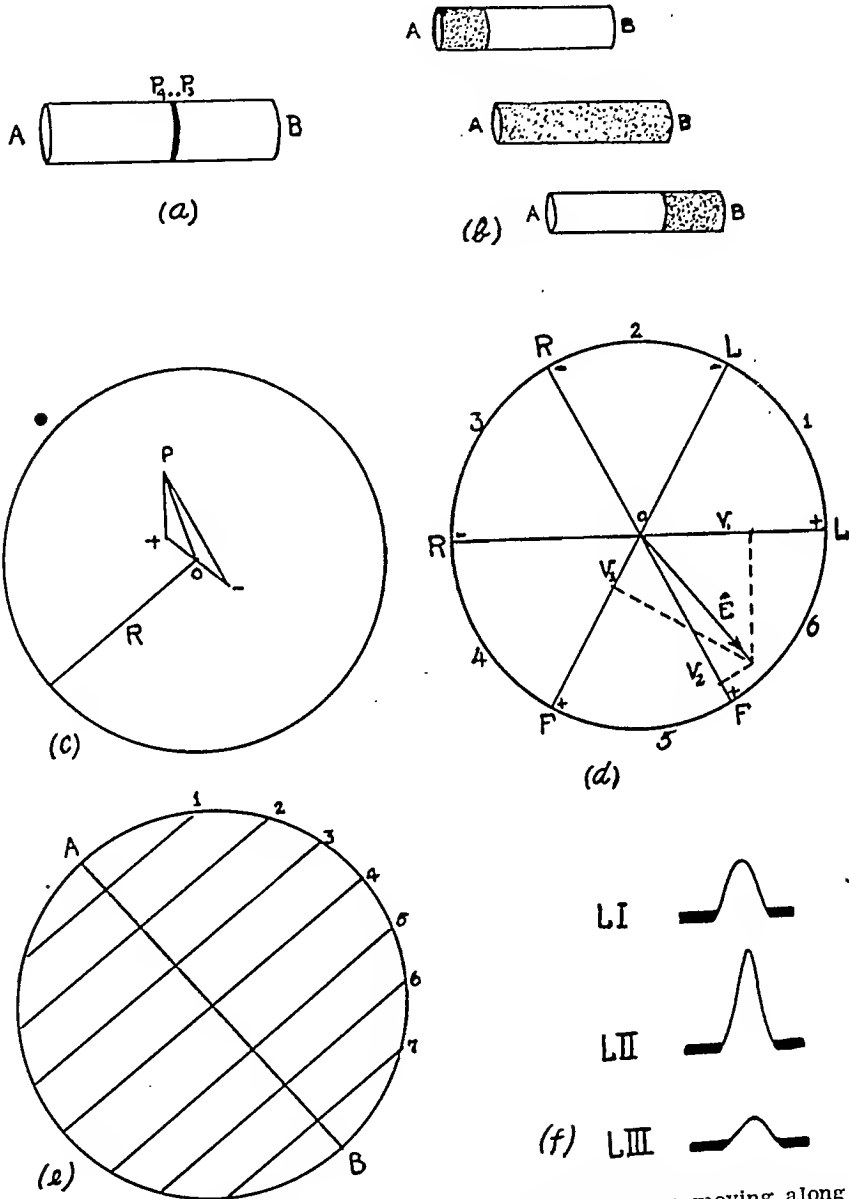


Fig. 2.—(a) The visualized boundary of the accession wave moving along the cell AB in the direction of B. (b) The nose of the regression wave appearing first at the stimulated end A of the cell (upper diagram), and reaching the end B ahead of the appearance of the tail at A (middle diagram). The lower diagram shows the tail of the regression wave reaching the end B. (c) Showing a spherical conductor of the radius R with a doublet at its center. (d) The triaxial reference system with the instantaneous electrical axis \hat{E} translated to the origin O. V_1, V_2 , and V_3 are the projections of \hat{E} upon the reference axes RL, RF, and LF. (e) A spherical mass of cardiac muscle stimulated at the point A. The numbered lines illustrate successive boundaries of the accession wave during its spread in the direction of B. Boundary 4 is a great circle, at which time the potentials (shown in the neighboring diagram) are maximum. (f) The accession potential differences produced by stimulation of the muscle mass shown in (e). See text.

place. Essentially, the change consists of a second reversal of polarity and is referred to as regression. The apparent movement of the second reversal over the cell is called the regression wave. The rate of regression at a point (or of a single element of membrane) is much slower than the rate of accession at a point. The velocities of the two waves, accession and regression, tend to be like and uniform.

In the region of the cell where accession is in progress (Fig. 2, *a*), a succession of interfaces cuts the membrane at right angles, one interface for each phase of polarity reversal. If the rate of reversal at a point is sufficiently rapid, so that the length p_3p_4 of accession is practically instantaneous, we may let ϕ_1 and ϕ_2 denote the respective moments of the resting and the excited double-layers.* Consequently, the accession potential is directly proportional to the constant given by the sum of ϕ_1 and ϕ_2 .

*From eqn(2-8) we get for the accession potential V_a

$$(2-9) \dots V_a = (\phi_1 + \phi_2) \int \int_S d\omega = (\phi_1 + \phi_2) \Omega$$

where ϕ_1 and ϕ_2 are the respective moments of the resting and the excited double-layers, and where Ω is the solid angle subtended twice (at the field point at which V_a is measured) by the boundary of the resting and the excited double-layers. Outside the cell the magnitude and the sense of Ω are the same, respectively, with each subtending, whereas they differ respectively with each of the two subtendings at an inside point. In the particular case where $\phi_1 = \phi_2$, V_a at any outside point is given by $2\phi_1\Omega$, and at any inside point in the plane of the wave, V_a is zero. In the particular case where $\phi_2 = \phi_1/2$, V_a at any outside point is $3\phi_1\Omega/2$, and at any inside point in the plane of the wave $V_a = -\pi\phi_1$.

In general, the variety of surface over which the integral of eqn(2-9) is taken will be one of three kinds, a first, a second, and a third. A surface of the first kind is defined as closed, and the integral vanishes, so that V_a is zero. A surface of the second kind is defined as bounded by one closed curve situated at the epicardial or the endocardial surface of the ventricles, and it is by this closed curve that the solid angle is subtended. A surface of the third kind is defined as bounded by two or more closed curves, and V_a is given proportionally by the sum of two or more solid angles reckoned with their proper sense and subtended by whatever number of closed curves are formed upon the ventricular surfaces.

The regression potential V_r at any point outside the lamellar source-sink distribution is given by³

$$(2-10) \dots V_r = \int \int_S (\phi_2 + \phi_1) \frac{\cos\theta}{r^2} ds$$

where ϕ_1 and ϕ_2 are the respective moments of the resting and the excited types of double-layer; r is the distance from the surface element ds to the field point at which V_r is measured; and θ is the angle made by r and the outward drawn normal to ds . In general, the values of the moments differ both with respect to one another and with respect to one lamella as compared with another. At any given instant during regression, the source-sink distribution is composed of lamellae of the first, second, and third kind, singly or in combination. If all lamellae are of the first kind, the integral vanishes and V_r is zero. The boundary of lamellae of the second kind and the boundaries of lamellae of the third kind are all closed curves upon the endocardial and epicardial surfaces of the ventricles. The regression potential, except for a proportional factor, is given by the sum of the solid angles subtended by the aggregation of closed curves. The potential of a zone of injury or ischemia is likewise dependent upon an aggregation of closed curves constructed upon the ventricular surfaces (Fig. 9).

Evidently, the important conclusion follows that the accession potential, the regression potential, and the injury potential depend only upon the activity of the muscle units at the ventricular surfaces, and are independent of the activity of the muscle units between these surfaces. In the case of local muscle death, the residual living muscle possesses a new and abnormal surface adjacent to the dead region, a surface at which certain of the closed curves must lie. The general conclusion which states that the normal or abnormal electrocardiogram may be reckoned from an aggregation of closed curves constructed upon the muscle surfaces is further supported by the well-known physical fact that the field strength E at any field point outside a distribution of the kind herein considered may be expressed not only by the negative gradient of scalar potential, but also by the sum of a number of vectors, each of which is given by the curl of the curve-potential of a closed curve multiplied by the respective moment.⁶

If the accession wave, having commenced at A, reaches B before regression begins, the excited double-layer is closed. Thus, everywhere outside the excited cell the potential is zero, and, everywhere inside, the potential is $4\pi\phi_2$.

Fig. 2, *b* illustrates the situation encountered during regression. In the upper diagram, regression has commenced at the end, A, of the cell, and the front of the regression wave is advancing in the direction of B. The second reversal of polarization is occurring throughout the shaded region. In the center diagram, the front of the wave has reached B before the tail of the wave appears at A. Here, the length of the regression wave exceeds the length of the course over which the wave appears to pass. Consequently, the whole surface of the cell is in the process of reversing its membrane polarity. In the lower diagram, the tail of the regression process is seen advancing in the direction of B. Throughout the unshaded regions, the subdivision of the cell is in the excited state (upper diagram) and in the resting state (lower diagram).

Throughout the shaded regions of the diagrams, it may be regarded that there is a succession of double-layer boundaries in pairs. The two double-layers associated with any one pair of boundaries differ in that their polarities with respect to the two sides of their membranes are unlike. They likewise differ in the configuration of their surfaces, i.e., one is concave toward A and the other is concave toward B. Each pair of boundaries defines a lamina of source-sink distribution which defines the local subtotal change of polarization. The total distribution is said to be lamellar. The electrical moments of the various laminae differ, inasmuch as the rate of regression at a point is not constant.* The regression potential is, therefore, a function of the rate of regression at a point.

The deflections on the completed record produced by regression are called the regression deflections, whereas those produced by accession are called the accession deflections.

The foregoing considerations make it clear that a cell in the resting or in the excited electrical state produces no outward electrical manifestations. Consequently, all of the normal electrical manifestations of the heartbeat occur while the heart's cells are in the process of passing from the resting into the excited state, and again while the cells are in the process of passing back from the excited into the resting state.

Because of more or less obvious technical difficulties, the electrical effects of a single cardiac muscle cell cannot be recorded. A mass of cardiac muscle immersed in an extensive homogeneous conducting medium acts, however, in a manner altogether similar to that described for the single cell.⁵ As the accession wave spreads from one cell to another in a direction everywhere away from the point of stimulation,

*See footnote page 781.

the effective boundaries of the double-layers move, or appear to move, along the limiting surface of the muscle mass, and the solid angle subtended by them is equivalent to the sum of all the solid angles subtended by the many boundaries of all the double-layers of all the cells which are involved by the accession process at the instant considered.

For the purpose of recording the potential at a point, one electrode, the exploring, is placed at a point in the conductor near the muscle under investigation, whereas the other electrode, the indifferent, is placed at a relatively remote point at or near the surface of the conductor. Under the circumstances, the potential at the indifferent electrode is relatively small in comparison with simultaneous values of the potential at the exploring electrode. Consequently, the effects on the completed record may be regarded as characteristic of the potential fluctuations at the exploring electrode only.² This method of leading is comparable to the method now widely used for recording the so-called chest leads in man, where the exploring electrode is placed at some desired point on the precordium and the indifferent electrode is placed on one of the extremities.

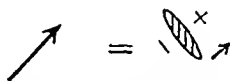
When recording the so-called extremity leads, Lead I is recorded from the upper extremities, Lead II is recorded from the right arm and left leg, and Lead III is recorded from the left arm and left leg. The extremities involved are regarded as mere continuations of the lead wires from the galvanometer. Consequently, the points on the conductor actually under investigation are R at the right shoulder, L at the left shoulder, and F at the symphysis pubis.

With respect to the three points R, L, and F, the electrical forces in the various elements of the accession or the regression wave act as if they were concentrated within a small region at the center of the frontal plane of the body, in the periphery of which the three points lie. Since each force may be represented as a vector,³ the sum of all forces at an instant must give a vector, the instantaneous cardiac electromotive force of which we may denote by \hat{E} . If the instant under consideration is within the auricular or the ventricular accession interval, \hat{E} is known as the instantaneous axis of accession. When the position within the heart (at any instant) of the accession wave is known, it is an easy matter to construct \hat{E} in the proper direction in space with a proportional magnitude. Let us suppose that the accession wave at an instant is in the form of half a tennis ball, expanding outward through cardiac muscle from a point of stimulation. The cut edge of the tennis ball corresponds to the circular boundary of the wave which necessarily resides at the surface of the muscle mass in which the wave is traveling. In effect, the source is distributed over the advancing surface of the wave (outer surface of the hemishell), and the sink is distributed over the trailing surface of the wave (inner surface of the hemishell). We next consider the imaginary plane surface denoted by S, which is circum-

scribed by the wave boundary (cut edge of the hemishell). The imaginary plane, S , is regarded as polarized in a sense similar to that of the wave. \hat{E} always lies perpendicular to S , and is directed away from the negative, toward the positive, side of S . The length or magnitude of \hat{E} is then constructed equal in units of length to the area of S in units of area. By construction, it is clear that the instantaneous cardiac electromotive force \hat{E} is independent of the configuration of the surface of the accession wave, and depends, in a proportional way, only upon the position in space of, and the plane area included by, the boundary of the wave. The foregoing construction is summed up in the simple and important relation⁸

$$(2-18)^* \dots \quad \hat{E} = S\hat{e},$$

or



*It is desired to know the effect upon the extremity leads of an arbitrary open double-layer. For this purpose let us assume that the extent of the conductor (body trunk) is limited to the volume of a large sphere of radius R (Fig. 2, c). The effect of the limiting surface of the conductor upon the value of the potential is such that the latter must be distributed everywhere within the interior and yet vanish everywhere outside. The potential of a doublet in an infinite conductor is described by relation (2-6). From this relation an expression may be obtained which satisfies the given boundary conditions. A fundamental equation of theoretical physics states that the electric intensity \hat{E} is equal to the negative gradient of scalar potential; that is,

$$(2-12) \dots \quad \hat{E} = -\nabla V$$

where, for our present purpose, the operator ∇ is equivalent to

$$\hat{r}_1 \frac{\delta}{\delta r} + \hat{\theta}_1 \frac{\delta}{r \delta \theta}.$$

Here, \hat{r}_1 and $\hat{\theta}_1$ are unit vectors in the directions of r , increasing, and θ , increasing, respectively. Thus the components of the electric intensity are given by the expressions

$$E_r = -\frac{\delta V}{\delta r}, \text{ and } E_\theta = -\frac{\delta V}{r \delta \theta}.$$

Eqn(2-12) shows that, if the electric intensity vanishes, the potential vanishes. For the large spherical conductor of radius R , the component of the gradient in the direction of θ , increasing, is, by symmetry, everywhere tangent to the surface of the conductor. Thus, in order to adapt eqn(2-6) to the given boundary conditions, we have only to consider the component of the gradient in the direction of r increasing. That is,

$$(2-13) \dots \quad E_r = -\frac{\delta V}{\delta r} = -\frac{\delta}{\delta r} (\phi \frac{\cos \theta}{r^2}) = 2\phi \cos \theta \frac{1}{r^3},$$

and, if the right-hand member is to vanish when $R = r$, we must have for our solution an expression which, when differentiated with respect to r , gives $2\phi \cos \theta / r^3 - 2\phi \cos \theta / r^3$. Moreover, eqn(2-13) shows that our original solution is the first term of the solution sought. For the second term let us try $\phi \cos \theta \frac{2r}{R^3}$. Then

$$-\frac{\delta}{\delta r} (\phi \cos \theta \frac{2r}{R^3}) = -2\phi \cos \theta \frac{1}{R^3}.$$

Consequently,

$$(2-14) \dots \quad V = \phi \cos \theta \frac{1}{r^2} + \phi \cos \theta \frac{2r}{R^3} \\ = \phi \cos \theta \left(\frac{1}{r^2} + \frac{2r}{R^3} \right),$$

and is the solution sought. Let us now replace the doublet in the spherical conductor by the arbitrary curved surface of accession double-layer S . For simplicity we may assume that the boundary of the double-layer is circular, and thus circumscribes a plane area S , the center of which coincides with the center of the large conductor. Actually, it is immaterial whether the contour of the double-layer is curved or plane or of some other form, or whether its boundary is circular or of some other form.

(Footnote continued on next page.)

where \hat{E} appears as a vector and S as the magnitude of the unit vector \hat{e} , drawn in the direction of the outward normal to the positive surface of S . Having determined \hat{E} in this manner, it is an easy matter to visualize geometrically the effects produced by \hat{E} at the instant under consideration on the potential differences recorded in the three extremity leads.

In any instant at which \hat{E} exists, the effect on the extremity leads is described, in a proportional way, by the projections of \hat{E} upon the lines of the leads. To illustrate; let the so-called lead lines, RL for Lead I, RF for Lead II, and LF for Lead III, form a triaxial reference system (Fig. 2, *d*). The reference axes are seen to divide the frontal plane of the body into sextants. Each reference axis has a positive and a negative half, divided by the origin O . The factor which determines the sense of the half-axes is the arbitrary method adopted for recording the "standard" extremity leads. Thus, the method adopted for recording Lead I is such that, when the potential at L is positive with respect to the potential at R, the potential difference recorded produces an upward (positive) movement on the completed record. Likewise, if the potential at L is negative with respect to that at R, the potential difference recorded produces a downward (negative) movement on the

The elementary potential dV_a at any field point nearby is, according to eqn(2-9), given by

$$dV_a = (\phi_1 + \phi_2) \frac{\cos\theta}{r^2} ds$$

Here, the plane area S over which integration is to be performed is equivalent to the open spherical surface of double-layer, inasmuch as their boundaries are coincident and the strength and polarities of each are respectively identical. For the potential at any point in the conductor of radius R we have²

$$(2-15) \dots dV_a = \phi \cos\theta \left(\frac{1}{r^2} + \frac{2r}{R^3} \right) ds$$

where ϕ in this relation is taken for $\phi_1 + \phi_2$. Since we are interested only in values of the potential at points upon the surface of the conductor where $r = R$, eqn(2-15) reduces to³

$$(2-16) \dots V_a = \frac{3\phi}{R^2} \iint_S \cos\theta ds$$

Let V_1 and V_2 denote the values of the potential at the field points p_1 and p_2 , respectively, and let p_1 and p_2 be chosen at the termini of the diameter of the spherical conductor which passes normal to, and through the center of, S . Moreover, let p_1 and p_2 be chosen in such a way that when one is stationed first at the former, and then at the latter, point, upon looking along the diameter, he views first the source and then the sink of the accession double-layer. The electromotive force \hat{E} across p_1 and p_2 may now be determined from eqn(2-16). By definition, the magnitude of \hat{E} is $V_1 - V_2$. Also,

$$V_1 = \frac{3\phi}{R^2} \iint_S ds$$

and

$$V_2 = -\frac{3\phi}{R^2} \iint_S ds$$

The value of $\cos\theta$ in these expressions is unity and minus unity, respectively. Thus, the relation which describes the electromotive force of the accession double-layer is

$$(2-17) \dots \hat{E} = \frac{6\phi S}{R^2} \hat{e}$$

where S is the plane area or analytic surface circumscribed by the boundary of the accession double-layer, and \hat{e} is a unit vector in the direction of the outward drawn normal to the positive surface of S . In eqn(2-17) \hat{E} has the direction of \hat{e} and the magnitude $6\phi S/R^2$. If we neglect the constant $6\phi/R^2$, we obtain the simple relation

$$(2-18) \dots E = S\hat{e}$$

which is useful in defining (in a proportional way) the electromotive force of accession. Here, E is equal in units of length to the area of S in units of area.

completed record. If the potential at F is positive with respect to that at R or at L, the potential differences recorded in Leads II and III produce upward (positive) movements on the completed record.

Let us suppose that \hat{E} in Fig. 2, *d*, is proportional to the accession electromotive force at a given instant. The projections of \hat{E} upon the three reference axes describe the potential differences V_1 , V_2 , and V_3 . The movement in all three leads is upward (positive) and is greatest in Lead II and smallest in Lead III. In order that \hat{E} in the reference plane may describe the full value, proportionally, of the effects of the accession wave, the boundary of the wave must lie in some plane perpendicular to the plane of the reference system. Inasmuch as the boundary of the wave is not restricted in this manner, the vector \hat{E} is not restricted to the plane of the reference system. In order to indicate the electromotive force which is not restricted to the plane of the reference system, we may prefix the letter *s* before the vector, indicating a spatial axis (free to move in three-dimensional space). Accordingly, the vector \hat{E} is always taken as the projection of $s\hat{E}$ upon the plane of the triaxial reference system. Obviously, if $s\hat{E}$ is normal to the frontal plane, \hat{E} is zero. Consequently, electromotive forces directed normal to the frontal plane of the body do not affect the extremity leads. In the particular case in which $s\hat{E}$ lies in the frontal plane, $\hat{E} = s\hat{E}$.

We are now in position to ascertain the effects on the extremity leads which occur during cardiac accession. Let us simplify the problem by substituting for the heart a spherical mass of cardiac muscle (Fig. 2, *e*). Let us suppose that stimulation occurs at A. Successive positions of the wave boundary appear in the order numbered as the wave approaches B. Here, the points A and B are regarded as lying in the triaxial reference plane, so that $s\hat{E} = \hat{E}$. Moreover, the magnitude of \hat{E} increases progressively, reaching a maximum at the time at which the boundary of the wave forms a great circle. Thereafter, the magnitude of \hat{E} decreases progressively to become zero as the wave reaches B. The direction of \hat{E} is constant during the accession interval, and is such that \hat{E} occupies the sixth sextant. During the accession interval, the terminus of \hat{E} may be regarded as tracing out a segment of the line AB twice, commencing and ending at the origin O of the triaxial reference system.

Keeping the foregoing factors in mind, the potential differences produced on the extremity leads throughout the accession interval may be visualized by inspection of Fig. 2, *d*. The form of the deflections is shown in Fig. 2, *f*. Each group of three potential differences determined on the triaxial reference system by a given magnitude of, and direction of, \hat{E} defines a group of three simultaneous ordinates under the curves of Leads I, II, and III. As the actual accession wave progresses in the heart, $s\hat{E}$ varies continuously in magnitude and direction throughout three-dimensional space.

SECTION III

FURTHER CONSIDERATIONS OF CARDIAC ACCESSION

The present state of our knowledge of the path by which the accession wave spreads over the heart permits only an approximation of the manner in which the P and QRS deflections are formed. There appear to be at least three distinct advantages, however, in attempting an approximation or synthesis of the kind herein undertaken. It will serve, first of all, as the introduction of a method by which a more detailed synthesis can be made when more data are known; it will serve, secondly, as a means of pointing out the more important factors upon which the form of the accession deflections depends; and, thirdly, it will offer a reference scaffold with respect to which certain valuable inferences may be drawn regarding the abnormal electrocardiogram.

Let us assume that the position of the heart within the chest is normal, and halfway between the vertical and horizontal; that the specific conductivity of the body is normal; that the normal order of accession occurs; and that the order is known. It then becomes possible to estimate the proportional magnitude and direction in space of the instantaneous axis $s\hat{E}$ of cardiac accession at various critical moments during the accession (P and QRS) intervals. These data will, in turn, give the imaginary path described in space by the terminus of $s\hat{E}$. The path thus described during the auricular accession interval is called the P $s\hat{E}$ -loop, whereas the path described during the ventricular accession interval is called the QRS $s\hat{E}$ -loop. These loops, including the T $s\hat{E}$ -loop, are referred to collectively as the vectorecardiogram. When their form has been determined analytically it is an easy matter to visualize geometrically the form of the extremity leads.

QRS

The accession wave invades the junctional tissues (A-V node, His bundle and branches, and the Purkinje network) during the downstroke of the P deflection. This fact is obvious, for the A-V node must be reached at the time when auricular accession is approximately half complete. The velocity of the accession process through the Purkinje network has been estimated at ten times that at which it spreads through the auricular muscle.

Let us consider further the relation,

$$(2-18) \dots \quad s\hat{E} = S\hat{e},$$

where $s\hat{E}$ is the spatial cardiac electromotive force; S is the imaginary plane circumscribed by the boundary of the ventricular accession wave, and is considered polarized in the same sense as the wave; and \hat{e} is a unit vector in the direction of the outward drawn normal to the positive surface of S . When two or more vectors are added to give a resultant vector, the members of the sum are referred to as the components of

the resultant vector. A vector is, therefore, equal to the sum of all its components. Thus if

$$(3-1) \dots \quad s\vec{E} = S_1\hat{e}_1 + S_2\hat{e}_2 + S_3\hat{e}_3 \dots \text{etc.}$$

each member on the right-hand side is a vector quantity representing a component of the resultant electromotive force $s\vec{E}$. Each of the analytical areas $S_1, S_2, S_3 \dots \text{etc.}$, is circumscribed by a separate boundary of the accession wave. The number of these boundaries existing simultaneously determines numerically the number of such areas. On the other hand, $\hat{e}_1, \hat{e}_2, \hat{e}_3, \dots \text{etc.}$, are unit vectors drawn in the direction of the outward normals to the respective positive surfaces of the analytical areas.

During the brief period in which the accession wave is passing through the junctional tissues, there is an analytical area S in the cross section of each Purkinje fiber, and the cardiac electromotive force $s\vec{E}$ is given according to eqn (3-1); that is, by the sum or resultant of all such component forces existing at the instant considered. There appears to be no related displacement of the galvanometer fiber during the conduction interval. Presumably, the magnitude of $s\vec{E}$ is insufficient to affect the completed record. It follows directly that the onset of QRS occurs shortly after the instant at which the accession wave begins to invade the ventricular muscle.

Let us assume that ventricular stimulation takes place at many points simultaneously upon the endocardial surface of the ventricular muscle. An accession wave of hemispherical form must then develop about each point of stimulation. The boundaries of the many waves thus formed define as many analytical areas which may be looked upon as so many subendocardial islets.

If some of the Purkinje fibers have pierced the ventricular muscle, they lead to deep points of stimulation. Each of the accession waves which form about the deep points of stimulation must have the form of a spherical, closed surface. Each such surface must remain closed until it reaches, by expansion, the limiting surface of the resting muscle mass in which it is traveling. As long as the many spherical surfaces of accession remain closed, they can make no contribution to the heart's electrical field. In this respect the closed accession surfaces under consideration act in a way altogether similar to the single resting or excited cell. Consequently, the total effect will be the same, or nearly the same, as it would if stimulation took place at subendocardial points only.

A short interval later, the subendocardial islets become confluent, at which time two large shells, S_R and S_L (for the right and the left ventricle, respectively), are formed by the now continuous contour of the accession wave. The contour of either shell must be very nearly that of the homolateral endocardium, and have boundaries approximately coincident with those of the four valve openings. The four boundaries

thus indicated may be looked upon as forming a single analytical surface, S_1 , circumscribed by the inner edge of the auriculoventricular junction. Clearly, the positive surface of the analytical area S_1 is directed toward the ventricular apex.

If the distribution of the points of ventricular stimulation is not uniform, there must be a greater density of islets in the regions to which the distribution of Purkinje fibers is most dense. No such subendocardial regions have been demonstrated as yet, and we shall, therefore, omit a consideration of them. On the other hand, if some region of subendocardial muscle is stimulated relatively early, this region must have islets of relatively greater circumference.

For the moment, let us assume that there are no such regions of early stimulation. Consequently, all of the islets must have the same dimensions simultaneously. This is equivalent to regarding the area S_1 as made up of uniformly scattered particles, or of a uniform density. Before the subendocardial islets appear, the density of S_1 is zero. When the subendocardial islets expand and become confluent, the density of S_1 is unity. Consequently, the density, D , of S_1 may be regarded as increasing from zero to unity throughout the initial phase of ventricular accession. The electrical effect of the initial phase is defined by the relation

$$(3-2) \dots \quad s\hat{E} = D(S_1\hat{e}_1)$$

where \hat{e}_1 is a unit vector drawn in the direction of the outward normal to the positive surface of S_1 . During the initial phase of ventricular accession it appears that the magnitude of $s\hat{E}$ increases from zero to S_1 , at the end of which time the shells S_R and S_L are intact. Consequently, the terminus of $s\hat{E}$ traces out a path which is collinear with a line drawn from the center of the ventricular base toward the apex; that is, from the origin O of the triaxial reference system into the sixth sextant.

Anatomic studies have shown⁹ that the left main branch of the His bundle gives off "early" branches which supply the anterior basal region of the interventricular septum. There are no "early" branches of the right main branch of the His bundle. The right main branch travels for a considerable distance toward the apex of the right ventricle before giving off branches to the septum. From this it may be concluded that the specified subendocardial region of the left septal surface is a region of relatively early stimulation. The islets of this region are, therefore, of relatively large circumference during the initial phase of ventricular accession. The component electromotive forces generated by the region of early stimulation are directed, in the sthenic adult, upward and forward, toward the sternum. Because of the preponderance of the early septal forces, the initial segment of the QRS $s\hat{E}$ -loop bends in a nearly similar direction, after which the loop courses downward and to the left in its previously described direction toward the ventricular apex.¹⁰

During the subsequent, brief period of ventricular accession, the shells S_R and S_L expand in the direction of the ventricular epicardium and toward each other within the septum. The expansion is attended by a relatively small increase in the area S_1 , with a further motion of the terminus of $s\hat{E}$ toward the ventricular apex. Expansion of the shells continues until one of the shells makes contact with the epicardial surface at a point where the subjacent ventricular wall is thinnest. Let us assume that this point is on the anterior aspect of the right ventricle, about halfway from base to apex. At the epicardial point specified, the shell S_R necessarily develops a new boundary which, on further expansion of the shells, must itself expand rapidly in all directions over the anterior aspect of the ventricular chambers, only to converge promptly over the posterior aspect of these chambers toward a second, posterior, epicardial point, located where the subjacent ventricular wall is thickest.

We may denote by S_2 (Fig. 3, *b*) the plane analytical area circumscribed by the new boundary. Obviously, the positive surface of S_2 is directed toward the spine. Whenever the first and second analytical areas exist, $s\hat{E}$ is defined by the relation

$$(3-3) \dots \quad s\hat{E} = S_1\hat{e}_1 + S_2\hat{e}_2.$$

On first thought, the boundary of the second analytical area may appear to become confused with that of the first as the former sweeps over the epicardial surface of the ventricles. Let us consider the points of contact of the two closed curves. At first contact, there is only one such point, then two, and finally one again. At any instant when two points exist (see Fig. 3, *b*), we may connect them with the line AB and note that AB forms a common boundary segment closing both of the boundaries of S_1 and S_2 . In this way it may be observed that the dorsal motion of the second analytical area S_2 results in decay of the first analytical area S_1 .

Clearly, the circumferential variations of the areas S_1 and S_2 must, according to eqn(3-3), cause the terminus of $s\hat{E}$ to part from its course in the direction of the ventricular apex and sweep in a dorsal direction, at first increasing its distance from the origin, and then decreasing this distance to zero as the final direction of $s\hat{E}$ becomes that of a line drawn from the center of the heart toward a point on the posterior epicardial surface where the area S_2 vanishes.

It is possible in this manner to construct synthetically the path described in space by the terminus of $s\hat{E}$ during the QRS or ventricular accession interval. The path is the QRS $s\hat{E}$ -loop of the vectorecardiogram. The projection of the loop upon the triaxial reference plane (Fig. 3, *c*) is the QRS \hat{E} -loop of the vectorecardiogram. The figure also illustrates the relationship of the QRS \hat{E} -loop to the form of the QRS complex of the extremity leads.

An excellent idea of the position in space of the QRS \hat{E} -loop may be gained by bending a pipe cleaner into the form of the loop and casting a distant light upon it, so that its shadow is thrown upon a card upon which a triaxial reference system has been described.

Let us define the anatomic axis of the heart as a vector, \hat{H} , drawn from the center of the ventricular base toward the ventricular apex.

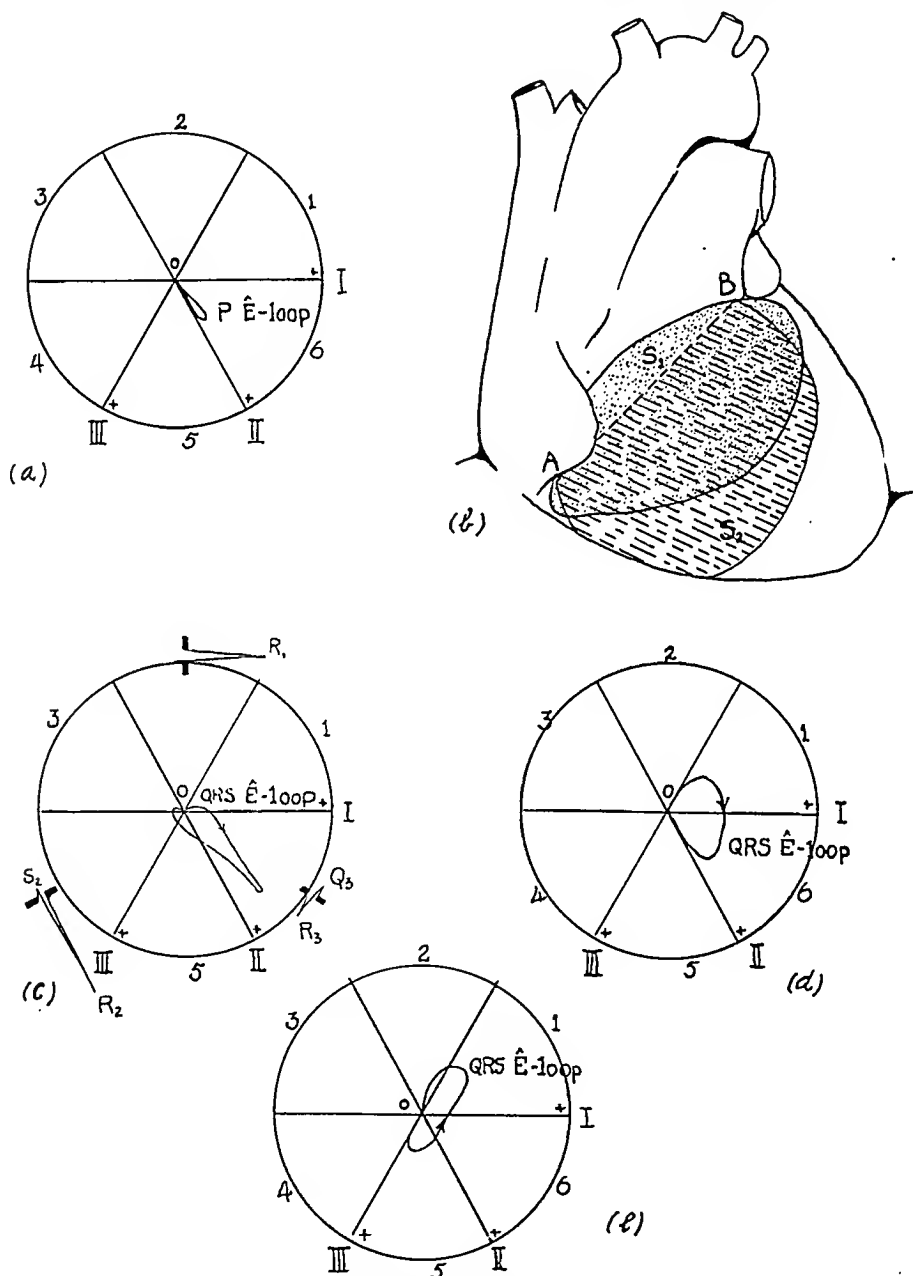


Fig. 3.—(a) Projection of the auricular accession effects upon the triaxial reference plane. They constitute the P \hat{E} -loop of the vectorcardiogram. (b) The analytical surfaces, or areas S_1 and S_2 of normal ventricular accession. (c) Showing the relationships between the QRS \hat{E} -loop of the vectorcardiogram, the triaxial reference system, and the associated deflections of the extremity leads. (d) and (e) Depicting the form of the QRS \hat{E} -loop as altered, respectively, by posterior and anterolateral infarcts. See text.

Positive rotation of the ventricles about \hat{H} is regarded as that motion which appears counterclockwise to an observer stationed at the terminus of \hat{H} , whereas negative rotation of the ventricles appears clockwise. It is highly advisable to study, in the manner suggested, the effects upon QRS of the extremity leads produced by elevation and fall of the free extremity of the loop. These motions will serve to explain clearly the highly complex variations of QRS of the extremity leads caused by motion of the heart as the result of breathing.

VENTRICULAR HYPERTROPHY AND BLOCK

An increase in the thickness of the ventricular walls affects the order of ventricular accession, or the form of QRS. The part played by this factor may be easily reasoned from a consideration of the part played by the normal thickness of the ventricular walls. It should be pointed out, however, that hypertrophy of one or both ventricles may produce a significant change of position of the ventricular mass, and thereby alter the form of QRS in this manner also.

Variations, whether normal or abnormal, in the architecture of the Purkinje network alter the manner of ventricular stimulation, the order of ventricular accession, and the form of QRS. The abnormal variations in the network are responsible for QRS changes ascribed to intraventricular block.

At times it is difficult, if not impossible, to ascertain whether one or a combination of factors, hypertrophy and block, is responsible for the QRS changes encountered. In any event, the ventricular accession interval is prolonged. Data on the velocity of the ventricular accession wave suggest that hypertrophy of the ventricles rarely prolongs the QRS interval beyond 0.10 second. Apparently, hypertrophy of the normally thin right ventricle rarely prolongs the QRS interval beyond 0.09 second.

In general, hypertrophy tends to produce an increase in the amplitude of certain of the QRS deflections, whereas intraventricular block tends to produce marked shurring and notching of these deflections.

During the analysis of bundle branch block curves, it is all-important to remember that, in the initial stages of ventricular accession, only the contralateral shell develops and is responsible for the initial QRS deflections. During the final stages, no homolateral shell develops because of the abnormal manner of (retrograde) stimulation. Thus, the broad, final QRS deflections are written by the abnormal accession of the homolateral ventricle.

ON LOCAL MUSCLE DESTRUCTION (INFARCTION)

Destruction of ventricular muscle, recent or old, local or diffuse, complete or incomplete, results in an absence, during accession, of electrical forces which were previously present within the dead region. The

character of the associated QRS changes depends, quite generally, upon the location and degree of the damage. For example, diffuse damage or fibrosis of uniform degree may be regarded as diminishing proportionally the numerical values of the analytical areas of ventricular accession, thus diminishing, in turn, the amplitude of the associated accession deflections without extensively changing their form.

On the other hand, the limits of a localized, severely damaged region define, at some time during accession, a new and abnormal boundary for one or both of the shells S_R and S_L , according to the points of contact of the shell or shells with the limits of the damaged region. Each new and abnormal boundary circumscribes a new and abnormal analytical area which, in turn, accounts for a new and abnormal component of the electromotive force $s\hat{E}$. Each component thus created supplies an additional term to the right-hand member of relations (3-2) and (3-3), according to when the new force exists.

It may appear paradoxical that the presence of a dead region, which is electrically inert, is accounted for by the addition in this manner of a new component electromotive force. The force arises, however, in consequence of the now unopposed forces in the diametrically opposite region of the involved shell. As a matter of fact, the new and abnormal force is itself the resultant of the newly unopposed forces of the involved shell.

Let us use the expression $S_3\hat{e}_3$ to describe an abnormal electromotive force of the kind under consideration. The analytical area S_3 is circumscribed by the boundary of the accession wave at the points of contact of the wave with the limits of the dead region. The positive surface of S_3 is directed toward the center of the involved ventricle, and \hat{e}_3 is a unit vector in the direction of the outward drawn normal to the positive surface of S_3 . Thus the direction of the new and abnormal electromotive force $S_3\hat{e}_3$ is along a line drawn from the center of the dead region toward the center of the involved ventricle. For example, if it is now assumed that the dead region is essentially subendocardial, the ventricular accession axis $s\hat{E}$ is defined, throughout the initial phase of accession, by the relation

$$(3-4) \dots \quad s\hat{E} = D(S_1\hat{e}_1 + S_3\hat{e}_3).$$

The frequent occurrence of local death in certain regions of the ventricular muscle makes them of particular importance, and they are considered separately in the discussion which follows.

The first region considered is ordinarily irrigated by subdivisions of the right coronary artery, and includes that part of the left ventricular wall which is adjacent to the diaphragm and the neighboring portion of the basal region of the interventricular septum. Infarction of this region is herein referred to as posterior infarction. As a general rule, infarction of the ventricular muscle involves at least the subendocardial half of the wall of the left ventricle, and, when the in-

involvement is transmural, the extent as observed from the epicardial surface is considerably less than when observed from the endocardial surface. The limits of a posterior infarct are ordinarily such that the hole cut out of S_L defines an area S_3 , with its positive surface directed upward, forward, and somewhat to the left, toward the center of the left ventricle. The projection of the new and abnormal force $S_3\hat{e}_3$ upon the plane of the triaxial reference system gives a vector which is directed into the first or second sextant. The preponderance of force in this direction distorts the initial stroke of the QRS \hat{E} -loop into the first sextant (see Fig. 3, *d*): The initial stroke of the QRS \hat{E} -loop, as it sweeps into that part of the first sextant which is adjacent to the second, writes the upstroke of R_1 and the downstroke of Q_2 and Q_3 . If the initial segment of the loop had swept into that half of the first sextant which is adjacent to the sixth, because of more septal and less diaphragmatic wall involvement, the initial phase of the QRS complex would have been characterized by $R_1R_2Q_3$ deflections. The magnitude of the abnormal force $S_3\hat{e}_3$ depends chiefly on the circumferential limits of the dead region, and, therefore, these limits are related proportionally to the amplitude of the abnormal Q_2Q_3 deflections. The duration of the force $S_3\hat{e}_3$ is primarily proportional to the extent of the infarct in the direction of the epicardial surface of the diaphragmatic wall and the right ventricular endocardial surface of the septum. Because a majority of posterior infarcts extend halfway or more through the wall, a significant Q_3 is taken as 0.04 second or more in duration.¹¹ Transmural infarcts of the posterior type may produce a single downward movement for QRS₃, a so-called QS₃ deflection. R_1 and Q_2 deflections are likewise present. It may safely be stated that many small posterior infarcts are not accompanied by characteristic $R_1Q_2Q_3$ deflections because of the small magnitude of the component force $S_3\hat{e}_3$. For an example of these QRS changes, see Fig. 4, *a*.

The second region considered is ordinarily irrigated by the anterior descending branch of the left coronary artery and is located in the anterolateral wall of the left ventricle. Infarction of this region is herein referred to as anterolateral infarction. The hole cut out of the shell S_L by the dead region defines a new and abnormal analytical area, S_4 , with its positive surface directed downward, backward, and somewhat to the right, toward the center of the left ventricle in such a way that the associated, abnormal component $S_4\hat{e}_4$ (as projected upon the triaxial reference plane) distorts the initial segment of the QRS \hat{E} -loop into the fourth or into the adjacent half of the fifth sextant (Fig. 3, *e*). The associated QRS complexes are characterized by initial $Q_1R_2R_3$ deflections. As shown in Fig. 3, *e*, R_1 is usually of small, whereas S_2 and S_3 are usually of large, amplitude. An essentially apical infarction of the region specified may cause the initial segment of the loop to sweep into that part of the fourth sextant which is adjacent to the third, thus producing a $Q_1Q_2R_3$ variety of initial QRS deflections.

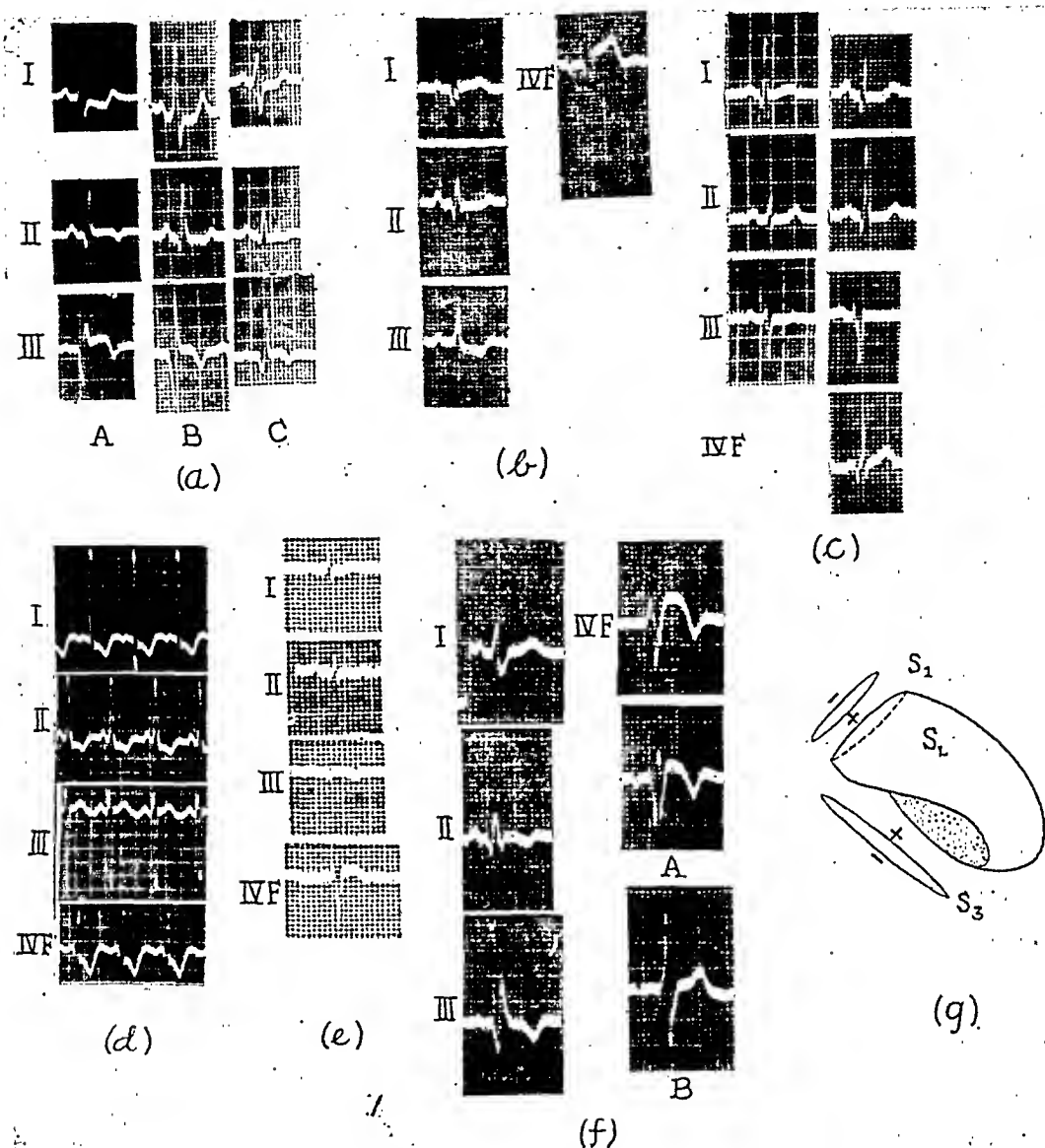


Fig. 4.—(a) Curves A and B were recorded nine months apart from a subject who had had a relatively recent posterior infarct. QRS is of the $R_1Q_2Q_3$ variety. Curve C was recorded from the same subject shortly after anterolateral infarction had developed. Note the reduction in amplitude and the slurring of R_1 , and the greatly reduced amplitude of Q_2 and Q_3 . At autopsy, both infarcts were seen to involve only the endocardial half of the ventricular wall. (b) A curve recorded on the day of death from a subject with hypertensive heart disease. The form of the curve illustrates changes caused by recent anterolateral infarction. At autopsy, the diameters of the infarct measured 7 cm. and 4 cm., respectively, on the endocardial and epicardial surfaces. (c) Curves recorded before and after the occurrence of strictly anterior infarction. The last attack of coronary pain had occurred one week before the right-handed recording. The Q_1 and the subsequent notch indicate that the precordial position 4 is superjacent to the margin of the infarct. Autopsy revealed that death had resulted from carcinomatosis of the liver. The healed, strictly anterior infarct measured 2.5 cm. in diameter and was confined to the endocardial half of the wall. (d) The clinical picture was characteristic of acute myocardial infarction. The changes are not considered diagnostic. However, the absence of QRS changes, together with the clinical picture, suggests that the infarct may be strictly anterior or posterior. The nature of the RS-T junction displacements (if due to injury) suggests involvement of the posterior wall. Preponderant hypertrophy of the left ventricle is probably responsible for all the changes shown. (e) Illustrating the changes associated with massive apical infarction. The minute R_1 may be ascribed to activation of the living subendocardial layer. At autopsy a few weeks after the recording, the large apical infarct was found to be of the transmural variety. (f) The changes are considered diagnostic of recent large posterior infarct and complete right bundle branch block. (g) Illustrating the manner of production of the QRS changes shown in (f). See text.

On the other hand, if an infarct of anterolateral location is somewhat basal, the first segment of the loop sweeps into that part of the fifth sextant which is adjacent to the fourth, and, consequently, Q_1 is of low amplitude. See Fig. 4, *b* for an example of these changes.

Inasmuch as newly unopposed forces in the diametrically opposite ventricular wall are directly responsible for the new and abnormal electromotive force associated with infarct, it is clear that the presence of the abnormal force depends, not only upon the infarct, but also upon the integrity of that region of the wall in which the newly unopposed forces lie. If, in addition to a posterior infarct, there is assumed to be an anterolateral infarct of similar dimensions, and the two infarcts are of diametrically opposite location, analysis requires the consideration of two new and abnormal component forces, $S_3\hat{e}_3$ and $S_4\hat{e}_4$. Furthermore, as a direct result of these assumptions, the two abnormal forces are of equal magnitude and inverse direction. Consequently, their sum is zero, and the effect produced on the form of QRS by the former, is annulled by that produced by the latter, infarct. Likewise, the effect of the latter, is annulled by the effect of the former, infarct. To be more exact, however, a result of this kind requires the additional assumption that the corresponding regions of the myocardium which are adjacent to the infarcts are activated simultaneously. Clinically, of course, an example of this sort is almost out of the question. It is reasonably common, however, to see typical QRS effects of one infarct annulled in part by the occurrence later of a second infarct. The QRS changes in curves B and C of Fig. 4, *a* illustrate just such a sequence of events. A "staircase" descending limb of Q_3 is occasionally produced.

A somewhat less common region for the site of infarction is the so-called strictly anterior region of the ventricular wall, made up of the anterior apical portion of the interventricular septum and the neighboring portion of the free wall of the left ventricle. This region is ordinarily irrigated chiefly by subdivisions of the anterior descending branch of the left coronary artery. Infarction of the region indicated is conveniently called strictly anterior. The hole cut out of S_L by the dead region defines an abnormal analytical area S_5 , with its positive surface directed posteriorly toward the center of the left ventricle. The new and abnormal component $S_5\hat{e}_5$ is perpendicular to the plane of the triaxial reference system. Consequently, its projection upon the frontal plane is zero, and there are no associated changes in the form of QRS of the extremity leads. The reader is referred to Fig. 4, *c* for an example of a curve of a strictly anterior infarct.

Of relatively rare occurrence is infarction of the strictly posterior wall of the left ventricle. The region involved is near the ventricular base. Its diametrically opposite position with respect to the apical portion of the septum has led some observers to refer to its infarction as "posterolateral" or "lateral." Infarcts in this region are more properly called strictly posterior infarcts. The muscle involved is ordinarily irrigated chiefly by subdivisions of the circumflex branch

of the left coronary artery. Like the case of strictly anterior infarct, the hole cut out of S_L by the strictly posterior infarct defines a new and abnormal area S_{∞} , coplanar to the plane of the triaxial reference system. The associated abnormal component $S_L\hat{e}_{\infty}$ is directed anteriorly toward the center of the left ventricle, perpendicular to the plane of the reference system. Its projection upon the plane is consequently zero, and no associated changes appear in QRS of the extremity leads. See Fig. 4, *d* for an example.

Occasionally, infarction may involve the entire apex of the left ventricle. The new and abnormal component $S_L\hat{e}_1$ has the inverse direction of $S_L\hat{e}_1$, and the former, therefore, tends to nullify the effects of the latter. When, in addition, it is recalled that the other component $S_2\hat{e}_2$ of normal accession acts chiefly in a direction perpendicular to the frontal plane of the body, it becomes obvious that apical infarction tends to establish an equilibrium of effective forces of ventricular accession. Consequently, the QRS \hat{E} -loop and its associated QRS deflections are characteristically of small dimensions (see Fig. 4, *c*).

In all of the above-mentioned varieties of infarction the shell S_L is involved. The failure of infarction to effectively involve the shell S_R is due presumably to the thinness of the wall of the right ventricle. Various studies on the coronary circulation indicate that a considerable volume of return coronary flow reaches the cavity of the right ventricle through numerous thebesian veins. It is held that, when the intra-arterial pressure falls as a result of diminished coronary flow, a reverse irrigation of the free wall of the right ventricle through the thebesian veins markedly diminishes the incidence of infarction of the free wall of the right ventricle. The interventricular septum, however, enjoys no such freedom from infarction, and is, therefore, best regarded as a complement of the free wall of the left ventricle.

The foregoing discussion places great importance on the initial QRS deflections in the diagnosis and location of infarction. The justification is primarily due to the consistent manner in which the electromotive force $S_L\hat{e}_1$ develops during the early stages of ventricular accession. The very nature of the development of the second component $S_2\hat{e}_2$ of normal ventricular accession makes for rather wide variability of the final QRS deflections of the extremity leads under normal as well as abnormal circumstances. Consequently, changes in the form of the final QRS deflections are of relatively little value in the diagnosis or location of infarction.

For a detailed example of the application of the analytical principles herein introduced, let us consider Fig. 4, *f*. The patient from whom the electrocardiogram was recorded was a white man, aged 52 years, who had been asymptomatic until he suddenly developed the clinical picture of acute cardiac infarction twenty-four hours before, and died five days after, the recording.

The duration of QRS is 0.12 second and S_1 is prominent and broad.

These changes are sufficient to justify the diagnosis of complete block of the right main branch of the His bundle.¹² When the right main bundle branch is blocked, the left ventricle undergoes accession first, and the order of accession is locally normal. Under these circumstances, the left ventricle may be regarded as writing the initial QRS deflections. Moreover, infarction must have the same, or nearly the same, effect upon the initial QRS deflections as it would have if right bundle branch block were not present. Inspection of Leads II and III shows conspicuous Q_2 and Q_3 deflections of the kind described as characteristic of posterior infarction. The fact that the duration of Q_3 is one-half as long as the duration of QRS suggests that the subendocardial infarct extends about halfway through the ventricular wall. The smooth, prominent downstroke of Q_3 suggests that the anterolateral wall of the left ventricle is intact. The electrical situation which underlies these changes is depicted in Fig. 4, *g*. The area S_1 is reduced to about half of its normal magnitude because of the absence of the shell S_R . The new and abnormal area S_3 is defined by the circumferential limits of a large infarct in the septum. Throughout the initial stages of ventricular accession, the cardiac electromotive force is defined by the relation

$$s\hat{E} = D(S_1\hat{e}_1 + S_3\hat{e}_3).$$

The initial segment of the QRS \hat{E} -loop sweeps into the adjacent halves of the first and second sextants and is approximately collinear with the negative Lead III reference axis. Analysis of the precordial leads and of the final ventricular deflections shown in Fig. 4, *f* is presented elsewhere. The autopsy observations are described in the legend.

A situation which is decidedly different from the one cited above exists for the analysis of left bundle branch block, in which the initial QRS deflections are of little or no help in the diagnosis of infarction. Here, the onset of QRS is of the $R_1R_2R_3$ variety, primarily because of the development of the shell S_R . If a small Q_1 is present, the block of the left side may be incomplete. It is conceivable that a $Q_1R_2R_3$ variety might be produced by the combination of left bundle branch block and a transmural infarct of the interventricular septum.

ON SEMIUNIPOLAR AND UNIPOLAR LEADS

When the two terminals of the galvanometer are connected with the body in such a way that one electrode is near the heart (upon the precordium) and the other is at a distant point (upon an extremity), the completed curve represents chiefly the fluctuations of the potential at the field point near the heart. The near contact is called the exploring electrode and the distant contact is called the indifferent electrode.

There are a considerable number of accepted methods of contacting the body with the galvanometer when recording semiunipolar and unipolar leads. The methods differ according to the position of the near contact and the position of the distant contact. When one of the ex-

limbs is used for the distant contact, the lead is said to be a semi-unipolar lead. When the distant contact is made with a central terminal which is connected in turn to each of the extremities R, L, and F, the lead is said to be a unipolar lead. The notation adopted for the semi-unipolar leads is CR, CL, and CF; C indicates that the exploring electrode (placed on the chest) is being paired with an indifferent electrode placed on one of the extremities R, L, or F. When the chest electrode is paired with the central terminal, the letter V designates the method. The precise position of the exploring electrode is designated by numerical subscript inserted after the capital letters or letter, as the case may be. Thus, CF₂ indicates a semiminipolar lead recorded by pairing the chest electrode, placed at the precordial position 2, with an extremity electrode placed on the left leg. In a like manner, V₂ indicates a lead recorded by pairing the chest electrode at position 2 with the central terminal. The accepted precordial positions are as follows. Position 1 is in the fourth intercostal space at the right margin of the sternum. Position 2 is in the fourth intercostal space at the left margin of the sternum. The other positions lie upon a line drawn from position 2 to the lateral margin of the apex beat, or to the junction of the left midclavicular line and the fifth intercostal space when the location of the apex beat cannot be ascertained. The line continues into the axillary region at the level of the junction specified. Position 3 is at the left parasternal line, position 4 is at the midclavicular line, position 5 is at the anterior axillary line, and position 6 is at the midaxillary line. Still another, and perhaps the most popular of the precordial leads, is denoted Lead V₆. Here, the precordial contact is placed just lateral to the apex beat (wherever it is found) and the extremity electrode is placed on the left leg. In all of the foregoing leads it is customary to arrange the galvanometer-body contacts in such a way that a positive potential at the precordial electrode produces an upward movement on the completed record.

The semiunipolar leads are continuously influenced to a variable degree by the fluctuations of the potential at the extremity to which the distant electrode is connected. At times, during interpretation of the semiunipolar leads, it is highly desirable to know the instantaneous potential at the extremity used in the recording. Let us denote by V_R , V_L , and V_F the instantaneous potential at R, L and F, respectively. Then, if

$$(3-5) \dots \quad LI = V_R - V_L,$$

by the adopted method of leading, we have

$$(3-6) \dots \quad LII = V_F - V_R$$

and

$$(3-7) \dots \quad LIII = V_F - V_L.$$

On the assumption that the electrical effects of the heartbeat act as if generated in a small region within the plane of the triaxial reference system, we have (by Kirchhoff's first law)

$$(3-8) \dots V_R + V_L + V_F = 0.$$

By adding equalities in eqns(3-5) and (3-6), we get

$$LI + LII = V_F + V_L - 2V_R.$$

But from eqn(3-8) we have $V_F + V_L = -V_R$. Hence, by substitution we get¹³

$$LI + LII = -3V_R$$

or

$$(3-9) \dots V_R = -\frac{LI + LII}{3}$$

for the potential at the right shoulder at an instant in terms of the potential differences in Leads I and II at a simultaneous instant.

In a like manner, we get

$$(3-10) \dots V_L = \frac{LI - LIII}{3}$$

and

$$(3-11) \dots V_F = \frac{LII + LIII}{3}$$

for the potentials at the left shoulder and at the symphysis pubis, respectively, in terms of simultaneous potential differences in the extremity leads. Obviously, in normal persons, when the heart is vertical and the potential differences are large in Leads II and III, the influence of the extremity potential V_F upon the CF leads may be considerable. In normal persons whose hearts are horizontal and the potential differences are large in Leads I and III, the influence of the extremity potential V_L upon the CL leads may be considerable.¹⁴

The accession potential at the precordial position is most conveniently defined by the relation (2-9); that is,

$$Va = (\phi_1 + \phi_2)\Omega,$$

where Va is the potential at the precordial electrode, ϕ_1 and ϕ_2 are constants denoting the electrical moments (intensity of polarization per unit of area of wave front) of the accession wave, and Ω is the solid angle defined and measured by the area of spherical surface cut off the unit sphere inscribed about the precordial point by the cone formed by drawing lines from the precordial point to every point upon the boundary of the accession wave. When the accession wave has more than one boundary at the instant considered, a corresponding number of

cones is formed, and the potential is regarded as proportional to the sum of the areas cut off the unit sphere by all the cones. The sense of the potential may be determined in the following way. Let us imagine that the accession wave is opaque, and that it carries a positive charge upon its advancing surface and a negative charge upon its trailing surface. An observer stationed at the center of the unit sphere (or at the tip of the precordial electrode), on looking through the base of the cone, must view the positive or the negative charge on the wave. The sense of the charge observed is the same as the sense of the potential. If multiple cones have been formed because the wave has more than one closed boundary, the observer at the center of the unit sphere looks through the base of one cone at a time, treating the wave as if all of the other cones and related boundaries were absent. The resulting sense of the potential will depend quite naturally upon the relative magnitude of the positive as compared with the negative solid angles. When the former magnitude is larger the sense of the potential is positive.

For example, let us consider the accession shell S_L (Fig. 5, *a*). P denotes the field point at which the precordial potential is measured. Clearly, the sense of the solid angle subtended at P by the boundary of the shell S_L is positive. Moreover, the potential at P would have the same value if all portions of the wave not included by the cone were removed. Consequently, that portion of the wave subjacent to P has a preponderant effect upon the potential at P . The value of the potential at the precordial electrode is determined chiefly by that arbitrary portion of the accession wave (or regression wave) which lies nearest the precordial electrode.¹⁵ This fact renders the interpretation of the unipolar (and semiunipolar) lead relatively simple.

Let us consider first the analysis of a normal curve recorded by Lead IVF. Under the circumstances, the electrical events in the apical regions of the ventricular walls dominate the form of the curve. When there are no electrical events in the subjacent ventricular wall, the form of the curve depends, for the most part, upon events occurring elsewhere. If these are scattered, but equidistant, or nearly equidistant, from the exploring electrode, the potential depends more or less equally upon all such events.

During the early stages of ventricular accession, the solid angle subtended at the tip of the precordial electrode by the boundary of the wave is often small and negative for a brief interval. Thus, a normal Q_4 results (amplitude = 0.2 millivolt or less, duration = 0.01 to 0.02 second). It appears highly probable that this deflection is caused by the relatively early invasion of the anterior basal region of the interventricular septum subjacent to the left ventricular endocardium. A similar Q_4 deflection is often seen normally in the fifth and sixth precordial positions, but not in positions 1, 2, and 3. The validity of the explanation is further supported by the fact that Q_4 occurs regularly in hearts which are the seat of hypertrophy of the left ventricle. The hypertrophy

produces a positive (counterclockwise) rotation of the ventricles about \bar{H} , and brings the endocardial aspect of the septal region specified into better view from the exploring electrode tip, which thus determines a more significant magnitude for the negative solid angle subtended. A Q_4 of this kind should be rare in children and in preponderant hypertrophy of the right ventricle because in these instances the positions of the ventricles are ones of relative negative rotation about \bar{H} .

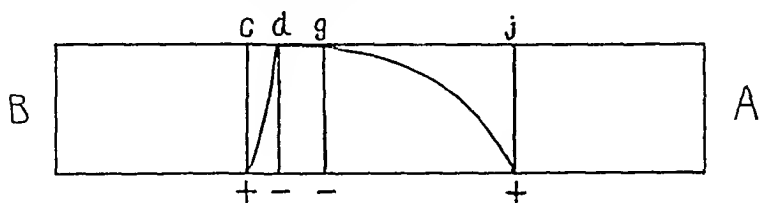
Continuation of accession soon results in approach of the wave toward p (the tip of the precordial electrode) through that region of the free wall of the left ventricle which lies subjacent to p . Obviously, the solid angle developed at p by the arbitrary subjacent wave rapidly becomes large in magnitude and positive in sign. Thus the usual, tall upstroke of R_4 results. This upstroke heralds the approach of the accession wave toward p as it passes outward through the ventricular wall. Moreover, the summit of R_4 signals the time of arrival of the wave at the subjacent epicardial surface. If, at this instant, the remainder of the ventricular muscle has been transgressed by the wave (not usually the case), the potential at p becomes zero and the downstroke of R_4 is recorded. Usually, the basal region of the free wall of the left ventricle is uninvaded at the instant specified, and a retreat of the wave in a direction away from p throughout the specified basal region results in a relatively small and negative solid angle. Thus, the downstroke of R_4 descends below the base line of the curve to form the descending limb of S_4 . With invasion of the free wall of the left ventricle, accession of the ventricles is complete, and the solid angle and, consequently, the potential vanish. The ascending limb of S_4 is thus recorded.

In a like manner and for like reasons, the form of T_4 depends upon the order of regression locally in that region which is subjacent to p . If, in the subjacent region, the subepicardial elements of muscle commence regression ahead of the subendocardial units in the immediate neighborhood, the potential at p is positive; or, if the subsurface units (subepicardial and subendocardial) in the subjacent wall commence regression ahead of the remaining subsurface units, the potential at p is positive and T_4 is an upward movement. In children T_4 may be inverted normally, and it is assumed that subepicardial units of the subjacent ventricular wall undergo regression relatively late in comparison with neighboring units at the epicardial and endocardial surfaces. The order of regression of the muscle units between the subsurface units is immaterial.* The effective onset of regression ordinarily begins before QRS is complete, and, consequently, the so-called RS- T_4 junction of the curve is frequently displaced upward (in adults) through a small distance ($= 0.1$ or 0.2 millivolt).

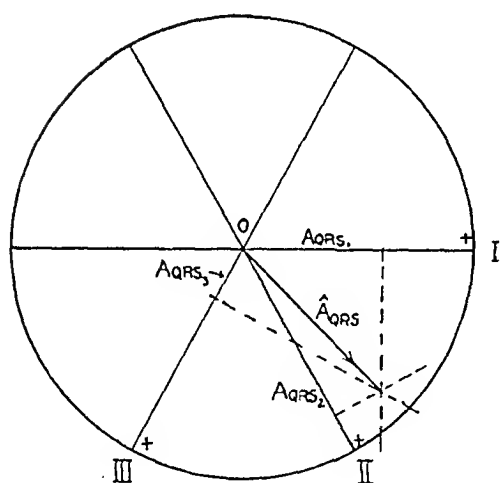
Under normal circumstances, using V leads, the QRS complex is regularly introduced by an R deflection at positions 1, 2, and 3. In an

*See footnote page 781.

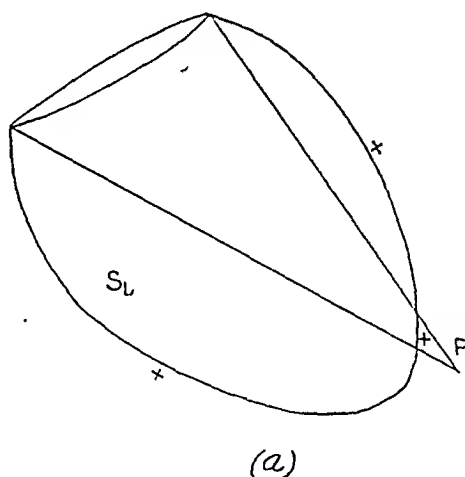
occasional instance the QRS complex may be comprised of a single QS deflection at position 1. The obvious explanation for the initially negative solid angle lies in the fact that an observer stationed at position 1 may, on looking through the base of the cone, observe the negative charge on the concave (retreating) surface of the accession shells S_R and S_L . The single QS deflection is encountered normally in the CF leads



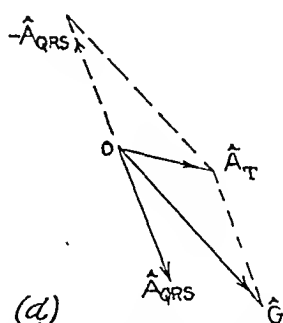
(b)



(c)



(a)



(d)

Fig. 5.—(a) Left ventricular accession shell S_L , with the proportional potential it produces at p , as measured by the solid angle subtended at p by the boundary of the shell. (b) Diagrammatic representation of the excitation wave ej at an instant during its passage along the muscle mass AB in the direction of B . (c) Showing the net areas A_{QRS1} , A_{QRS2} , and A_{QRS3} , plotted out along the axes of the triaxial reference system. The relationship between these areas and the manifest mean axis \hat{A}_{QRS} is likewise shown. (d) The geometric relationship of the manifest mean axes \hat{A}_{QRS} , \hat{A}_T , and \hat{G} . See text.

at positions 1 and 2. Here, the explanation is the same as that given for V leads, except that the leg potential (usually positive) favors the formation of the QS type of complex. Generally speaking, the amplitude of R of the precordial leads (semiunipolar and unipolar) normally increases from position 1 through position 4. At position 5 it may show a further increase (slight) or a decrease. At position 6 the amplitude of R is normally less than that encountered at position 5. The described sequence of normal variations is very important, inasmuch as limited damage in the subjacent ventricular wall may be recognized by a disturbance in the sequence, whereas one curve taken by itself is valueless.

We are now prepared to consider further the initial ventricular deflections of Fig. 4, *f*. Lead IVF shows that R has a rather broad upstroke which is probably not normal and which may possibly represent a low-grade, left-sided, intraventricular conduction defect. In this connection, a curve recorded from the patient shortly before death (not presented) showed complete heart block. The notch on the upstroke of S is part of the picture of right bundle branch block, or, to be more exact, is associated with the late aberrant spread of the accession wave into the right ventricle.

When recording curve A, Lead CF₂ was used. The minute R and the initial, sharp downstroke of QRS must represent accession of the left ventricle, for, in complete right bundle branch block, only the shell S_L exists throughout this period. Moreover, the effects under consideration may be said to represent, chiefly, accession of that part of the left ventricle which lies nearest to the exploring electrode; that is, effects of the anterior free wall of the left ventricle and the neighboring anterior region of the interventricular septum. The small R under discussion represents the approach in this region of a small area of wave in a direction toward the tip of the exploring electrode. The following, initial, sharp downstroke indicates that the electrode potential has suddenly become negative, an event which may be accounted for in the following way:

The shell S_L is, no doubt, intact (of unit density) at the time of the sharp downstroke (= 0.04 second after the onset of accession). Moreover, S_L undoubtedly has two large circular boundaries at this time, one which defines the normal area S₁ of reduced magnitude, and a second, abnormal area S₂ created by a large septal infarct. The solid angle subtended at the exploring electrode tip by the former boundary is positive when the latter boundary is supposedly absent. Likewise, the solid angle subtended at the same point by the latter boundary is negative when the former boundary is supposedly absent. Inasmuch as the actual potential at position 2 is given by the sum of the two solid angles multiplied by ($\phi_1 + \phi_2$), the resulting negative sense of the potential is actually accounted for, provided only that the infarct is relatively

large. The subsequent sharp upstroke heralds the approach of the accession wave in the subjacent free wall of the right ventricle. It occurs late (0.06 to 0.07 second after the onset of QRS), as might be expected when the right main branch of the His bundle is blocked.¹⁶ The final downstroke represents the retreat of the accession wave through the lateral free wall of the right ventricle.

Curve B (Fig. 4, *f*) was recorded with the exploring electrode in the fourth intercostal space just lateral to the left border of the heart; that is, over the anterior free wall of the left ventricle. Here, the detailed explanation of the QRS complex is the same as for the normal recording from this point, except that the slow upstroke of S is abnormal because of the delayed retreat of the accession wave in a direction away from the electrode tip toward the free wall of the right ventricle. The sharp upstroke of R confirms opinion derived from the extremity leads regarding the integrity of the anterolateral free wall of the left ventricle. We are as yet unable to interpret the abnormal final ventricular deflections.

SECTION IV

ON THE REGRESSION PROCESS AND THE MEAN ELECTRICAL AXES

The T or final ventricular deflection represents the electrical effect produced by spread of the regression process over the ventricular muscle. The onset of T in the various leads indicates the time at which the magnitude of the regression effect is sufficiently great to influence the completed record. For the extremity leads, this time may be considerably later than the time at which regression actually begins at some ventricular point.

There are certain striking differences in the form of T as compared with the form of QRS. Obviously, these differences represent certain differences in the characteristics of the regression wave, as compared with those of the accession wave.

Let us consider a graphic representation of the excitation wave, *cj* of Fig. 5, *b*, as the wave travels along the cylindrical mass AB of cardiac muscle. Stimulation has occurred at the end A, so that the wave *cj* is traveling, at the instant under consideration, away from A in the direction of B. The wave may be subdivided, for descriptive purposes, into three zones, *cd*, *dg*, and *gj*. Within the zones *Be* and *jA*, which lie, respectively, before and behind the excitation wave, the muscle cells are in the resting electrical state. The zone *cd* represents the accession wave within which the cells are in the process of passing from the resting into the excited electrical state. The cells within this zone are said to be undergoing the initial reversal of polarization. The length of the zone *cd* is equal to $v_0 t_0$, the product of the velocity v_0 of the accession wave by the time t_0 elapsing between the beginning and completion of accession at a given point. Within the zone *dg* the muscle cells are in the fully excited state; that is, the cells have undergone a change

(reversal) of polarization which is maximal for the present excitation. The actual length or duration of the excited state is determined by the time after accession at which regression begins. The effective length or duration of the excited state depends upon the time after accession at which effective regression begins. The former duration, unlike the latter, is independent of the rate of regression at a point. In so far as the completed record is concerned, an increased rate of regression at a point may shorten the effective duration, whereas the actual duration may remain unchanged. The zone gj represents the regression wave within which the muscle cells are in the process of passing back from the excited into the resting electrical state. The cells within the zone designated are undergoing a second reversal of polarization. The length of the zone gj, or the length of the regression wave, is equal to $v_0 t_1$, which is the product of the velocity v_0 of the regression wave by the time t_1 that elapses between the beginning and completion of regression at a point.

In Fig. 5, b, the slope of the curve within the zone cd and the slope of the curve within the zone gj represent the respective rates of the initial and the final reversal of polarization at a point. Presumably, each curve is of exponential form. It is observed that the rate of the initial reversal is greater than the rate of the final reversal. Throughout the zone dg, no change of polarization occurs, and the curve representing the rate of change has no slope or is horizontal. Clearly, the curve within the zone cd appears to be nearly straight in comparison with the curve within the zone gj; this difference is caused by the more rapid rate of change of polarization in the former as compared with the slow rate of change in the latter. The assumption that the electrical moment ($\phi_1 + \phi_2$) of the accession wave is constant is equivalent to the assumption that the length of the wave is very short, or that the initial reversal of polarization is, for all practical purposes, instantaneous.

Because of the tendency toward uniformity of physiologic activity by the various units of cardiac muscle, the order of accession tends to determine the order of regression. However, a local variation of this uniformity may alter locally the effective duration of the excited state, and, by so doing, alter the order of regression without affecting the order of accession.

The order of ventricular accession tends to determine the order of ventricular regression. The former determines the form of QRS, whereas the latter determines the form of T. Consequently, the form of QRS tends to determine the form of T. However, if there should occur a local variation in the uniformity of the effective duration of the excited state, the order of regression will not be the same as the order of accession, and the form of T will be altered by the local variation in effective duration of the excited state.

It is clear that, if the characteristics of the two waves, accession and regression, were identical except for polarity, and if the order of ven-

tricular accession determined completely the order of ventricular regression, and if the effects of accession were complete before those of regression commenced, the accession deflections (QRS) would be followed by regression deflections (T) of identical form except that the polarity of the corresponding deflections would be of unlike sign, one positive and the other negative.

Under normal circumstances, the resting states before and after a given excitation are comparable. Consequently, the total change of polarization produced during accession is comparable to the total change of polarization produced during regression. Any difference encountered, other than polarity, in the total effect produced during accession as compared with the total effect produced during regression may be ascribed, therefore, to a difference in the order of regression as compared with the order of accession. The area under the curve of QRS is equal to the product of the mean accession voltage by the duration of QRS, and is a measure of the total electrical effect produced by ventricular accession.¹⁷ Likewise, the area under the curve of T is equal to the product of the mean regression voltage by the duration of T, and is a measure of the total electrical effect produced by ventricular regression. Let us denote the area under QRS by A_{QRS_1} and the area under T_1 by A_{T_1} . Inasmuch as the ordinate under the curve is measured in microvolts and the duration in seconds, the areas A_{QRS_1} and A_{T_1} are measured in microvolt-seconds (= m.v.s.). According to the notation adopted for Lead I, the areas under QRS_2 and T_2 are denoted by A_{QRS_2} and A_{T_2} , respectively, and similar notation holds for Lead III. In general, an area of the kind under consideration has a sense, positive or negative, depending on whether the net area under the subdivision of the curve considered measures positive or negative.

If the numerical values of any two of the quantities A_{QRS_1} , A_{QRS_2} , and A_{QRS_3} are plotted out on the proper half of the corresponding reference axis, commencing at the origin O (see Fig. 5, c), they determine a vector quantity \hat{A}_{QRS} , of which each is a projection. The origin of \hat{A}_{QRS} is at O, and the terminus of \hat{A}_{QRS} is at the intersection of two perpendiculars drawn to the outward extremities of the plotted areas.

In so far as the triaxial reference plane is concerned, the magnitude of \hat{A}_{QRS} is a measure of the total electrical effect produced by ventricular accession, and the direction of \hat{A}_{QRS} is the direction in which the accession wave travels over the average element of ventricular muscle.

A vector quantity \hat{A}_T is determined from any two of the areas A_{T_1} , A_{T_2} , and A_{T_3} in essentially the same manner used for determining \hat{A}_{QRS} . The magnitude of \hat{A}_T is a measure of the total electrical effect produced by ventricular regression, and the direction of \hat{A}_T is the inverse direction in which the regression wave travels over the average element of ventricular muscle. Thus, if the order of ventricular accession determined

completely the order of ventricular regression, so that the course of the two waves was the same, we would have the relation

$$(4-1) \dots \hat{A}_{QRS} = -\hat{A}_T,$$

and the sum of the two vectors is zero. Inasmuch as relation (4-1) does not hold for the normal human electrocardiogram, it is clear that, even under normal circumstances, the order of ventricular regression is not the same as the order of ventricular accession. Consequently, there is a normal lack of uniformity in the effective duration of the excited state in various parts of the ventricular muscle at the epicardial and endocardial surfaces. The duration of the excited state in muscle layers between the subsurface layers is immaterial.* The sum of the vectors \hat{A}_{QRS} and \hat{A}_T gives a new vector, \hat{A}_{QRST} , or \hat{G} , which is a measure of the lack of uniformity in the effective duration of the excited state in various parts of the subepicardial and subendocardial muscle layers. In so far as the frontal plane of the body is concerned, the magnitude of \hat{G} is a measure of the total effect produced by the lack of uniformity in the effective duration of the excited state, whereas the direction of \hat{G} is that of a line along which the variations in the effective duration of the excited state are greatest.

The vectors \hat{A}_{QRS} and \hat{A}_T are known, respectively, as the manifest mean electrical axis of accession and the manifest mean electrical axis of regression. The vector \hat{G} is known as the manifest mean electrical axis of QRST, or as the gradient, which may be said to point toward regions in the ventricular muscle at the epicardial and endocardial surfaces in which the average duration of the excited state is greatest, towards regions in the muscle at these surfaces where the average duration is least.

Inasmuch as the vectors \hat{A}_{QRS} , \hat{A}_T , and \hat{G} are determined from measurements made on the extremity leads, the vectors are restricted to the plane of the triaxial reference system. It is clear, however, that the electrical forces in the ventricles are not thus restricted, and must have a set of three mean axes operating in three-dimensional space. In order to avoid confusion, the set of spatial mean axes are denoted $S\hat{A}_{QRS}$, $S\hat{A}_T$, and $S\hat{G}$, where the prefix S merely indicates three-dimensional space. Any one of the manifest mean axes is simply the projection of the corresponding spatial mean axis upon the plane of the triaxial reference system. For the relations connecting the three axes of both sets, spatial and manifest, we have

$$(4-2) \dots S\hat{A}_{QRS} + S\hat{A}_T = S\hat{G},$$

and

$$(4-3) \dots \hat{A}_{QRS} + \hat{A}_T = \hat{G},$$

respectively. At the present time our knowledge of the spatial mean

*See footnote, page 781.

axes must depend upon speculation based upon the known activities of their projections, the manifest mean axes. Nevertheless, the definitions herein offered for the manifest mean axes¹⁷ apply equally well to the spatial mean axes.

The triaxial reference system, which has been found useful in dealing with the instantaneous axis, is likewise useful in dealing with the manifest mean axes. Moreover, the triaxial reference system may be expanded into a tetraaxial reference system for dealing with the spatial mean axes, i.e., let a z-axis pass through the origin O, normal to the triaxial reference plane, and, according to custom, let the positive half of the z-axis lie dorsal, and the negative half ventral, to the triaxial reference plane.

The discussion which follows will deal only with the manifest mean axes \hat{A}_{QRS} , \hat{A}_T , and \hat{G} . We may write eqn(4-3) in the form

$$(4-4) \dots \quad \hat{A}_T = -\hat{A}_{QRS} + \hat{G},$$

which states that the mean axis of T is equal to the sum of two vectors, the inverse of the mean axis of QRS and the ventricular gradient. The relation clearly shows that the area under T depends upon two components, the area under QRS and the ventricular gradient. Any factor which alters the area under QRS will, by so doing, alter the area under T secondarily. Changes in T caused by changes in QRS are called secondary T-wave changes.¹⁷ On the other hand, any factor which alters the ventricular gradient will, by so doing, alter the form of T primarily without altering the form of QRS. Changes in T caused by alterations of the gradient are known as primary T-wave changes. In electrocardiographic interpretation it is a matter of great clinical importance to ascertain which T-wave changes are primary, secondary, or a combination of both.

For a geometrical interpretation of eqn(4-4), we may consult Fig. 5, *d*. Clearly, \hat{A}_T is the directed diagonal of a parallelogram of which $-\hat{A}_{QRS}$ and \hat{G} form two sides. It is to be recalled that all of the origins of the manifest mean axes coincide with the origin O of the triaxial reference system (not shown). Under most normal circumstances, the mean axes lie in the region defined by the sixth and the adjacent halves of the fifth and first sextants. The plotted points in Fig. 6 indicate the positions of the termini of 100 gradients as ascertained by measurement of electrocardiograms from as many normal adults. In each of the 100 normal adults, \hat{G} was found to lie nearly collinear with \hat{H} , the base-apex axis of the ventricles. The axis \hat{H} was ascertained directly from the subject's chest roentgenogram.*

A further consideration of Fig. 5, *d* shows that, if the terminus of \hat{A}_{QRS} is made to describe any arbitrary path whatever about O, while the gradient remains fixed, the terminus of \hat{A}_T describes a path of similar form about the terminus of \hat{G} . The second path, however, appears as if rotated through 180 degrees (when compared with the first), and

*Dr. R. H. Bayley, Dr. J. E. Holoubek, and Dr. A. B. Holoubek were co-workers in the preparation of these data (1940).

exists the greatest space rate of change of subnormal polarization during the resting, and again during the excited, state. It is clear that, until the injured zone extends to the epicardial surface, all of its lamellae are closed. Consequently, during the resting, and again during the excited, state, no field of injury exists outside of the ventricular wall. It is likewise clear that, when the injured zone is transmural, the injury potential outside the ventricular wall is a function of the difference between the subnormal change of polarization at the epicardial surface and that at the endocardial surface. The subnormal change of polarization in units between these surface layers is immaterial.²¹

The spatial axis of injury $s\hat{E}_i$ is proportional in length to the areas circumscribed by the boundaries of the open laminae of the injured zone, and is directed (during systole) from the center of the involved ventricle toward the center or centroid of the injured zone.

In stage *C* of Fig. 9, *a*, the area circumscribed by the epicardial boundary of the injured zone has expanded at the expense of the area circumscribed by the epicardial boundary of the ischemic zone. Consequently, the appearance of RS-T junction displacements (dependent upon the former area) are accompanied by a subtotal disappearance of primary T-wave changes (dependent upon the latter area). Obviously, as the accession wave traverses the subnormally polarized injured zone, the magnitude of the local accession forces is proportionally subnormal, and, consequently, QRS changes concurrently appear.

The initial development of local ischemia and injury may be regarded as proceeding to the stage (*C* of Fig. 9, *a*) at which a dead region is about to appear, and, being reversible, may be looked upon as producing the transient variety of electrocardiographic changes that are observed in certain patients with angina pectoris. However, if the process is regarded as introducing myocardial infarction, the zones specified are responsible for changes which are best described as evidence of impending infarction. The evolution through which the changes may proceed or the time they may last and yet be unattended by the appearance of a dead region (actual infarction) is not known. Clinicopathologic observations make it certain, however, that an evolution which stops short of the injury effects may exist for several weeks, and possibly several months, and be unattended by the development of a dead zone.¹⁹ If the evolution proceeds rapidly, and promptly reverses, the stage of RS-T junction displacement may be reached without the occurrence clinically of evidence which is considered characteristic of actual infarction.

Including the electrocardiographic changes herein described as evidence of impending infarction, the electrocardiographic evolution of myocardial infarction may be described in five fundamental stages: (1) the initial diversion of the gradient \hat{G} , which is a measure of the appearance of the primary T-wave changes; (2) the development of the axis of injury \hat{E}_i , a concurrent subtotal reversion of \hat{G} , and a concurrent

diversion of \hat{A}_{QRS} , which measure, respectively, the appearance of RS-T junction displacements, the subtotal disappearance of the primary T-wave changes, and the appearance of QRS changes; (3) the decay of \hat{E}_t , the concurrent second diversion of \hat{G} , and the concurrent subtotal reversion of \hat{A}_{QRS} , which measure, respectively, the disappearance of RS-T junction displacements, the reappearance of primary T-wave changes, and the subtotal disappearance of QRS changes; (4) the final reversion of \hat{G} , which measures the final disappearance of the primary T-wave changes; and, finally, (5) the permanent persistence of a diversion of \hat{A}_{QRS} and \hat{A}_T , which measure the permanent QRS changes and the permanent secondary T-wave changes.

Ordinarily, stage 1 is traversed rapidly in the case of infarction, so that the initial electrocardiograms display changes characteristic of stage 2 or stage 3. Stage 4 continues for a relatively long period of time, and the associated changes are usually referred to as evidence of healing of the infarction. In a single curve, the changes associated with stages 2 and 3 may closely resemble one another, and other clinical criteria must be used to ascertain the presence or absence of myocardial infarction. When stage 5 has been reached, infarction is said to be healed.

SUMMARY AND CONCLUSIONS

As pointed out more than a decade ago by F. N. Wilson and his co-workers, the well-established laws which define the flow of electric currents in homogeneous volume conductors are applicable to the interpretation of the electrical effects produced by the heartbeat with sufficient accuracy to be of (great) clinical usefulness. An analytical approach to the problem is herein made by a method of geometric visualization which should prove useful to those who are not familiar with advanced mathematics. A few footnotes are included; they contain some of the more profound aspects of the problem and support much of the material, but they may be neglected by those who are interested only in a clinical use of the analysis.

The properties of vectors are defined, and the three required manipulations are discussed. The characteristics of the electrical field are briefly considered in relation to a point source and in connection with the excitable cell. The instantaneous electrical axis is defined and its use illustrated.

Ventricular accession is considered inductively, and the critical formations of the QRS sE-loop of the vectorecardiogram are derived synthetically. Important relationships between the loop and the extremity leads are pointed out. The effects on the loop and those on the extremity leads produced by hypertrophy, block, and muscle death are analyzed. The unipolar and semibipolar leads are considered analytically.

The manifest and spatial mean axes are defined and discussed, with particular emphasis on their value in the interpretation of the primary

and secondary T-wave changes. Certain clinical and analytical manifestations of local ventricular ischemia are considered. It is pointed out that the primary T-wave changes which frequently attend acute nephritis in transient form and those which attend chronic hypertension in more permanent form are strikingly similar to those which indicate local ischemia of muscle that is ordinarily irrigated by the left coronary artery.

The electrical effects produced by an injured lamina are discussed in relationship to pericarditis and stab wounds of the heart. Finally, the electrocardiographic evolution of myocardial infarction is considered, and the similarity of certain early stages to certain late stages is stressed.

In order to accomplish the task, it became necessary to introduce much which is not new, but which is scattered within various sources that have appeared at intervals over a considerable period of time. The method of analysis, as set forth, has proved useful to the author over a period of years both for diagnostic and teaching purposes. Moreover, the uniformly accurate diagnostic results obtained, particularly in problems of local myocardial ischemia and infarction, appear to completely justify the adoption by Wilson, et al., of certain well-established physical laws for interpretation of the electrical effects produced by the heart-beat.

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Clinical Reports

COARCTATION OF THE THORACIC AORTA WITH AN ANEURYSM DISTAL TO THE OBSTRUCTION

REPORT OF A CASE

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IN A review of the literature up to September, 1942, only two cases of aneurysm of the aorta distal to a coarctation were found.^{1, 2} This paper presents a similar case in a 25-year-old white man.

CASE REPORT

D. Y., a 25-year-old white man, was apparently in good health until one year prior to admission to the Jewish Hospital in Philadelphia. At that time an increase in the size of the base of the heart was found during a routine physical examination. A roentgenogram revealed a prominence in the region of the aortic knob. Several serologic tests for syphilis were negative. One week before admission to the hospital the patient developed an upper respiratory infection, followed by a persistent cough. About 7 A.M. on the day prior to admission, the patient awoke with a feeling of malaise and pain in the left shoulder. During the day the pain became worse, stabbing in nature, and radiated over the precordium to the left upper quadrant and left loin. He was nauseated, but did not vomit. At 4 A.M. on the day of admission, the patient had a severe precordial pain and collapsed. He was admitted to the hospital at 5:20 A.M. on Feb. 20, 1943. There were no further contributory facts in the history.

Physiical examination on admission revealed a well-developed and well-nourished white man in severe pain. He was oriented and cooperative. The oral temperature was 102° F. The radial pulse rate was 90 per minute. The respiratory rate was 28 per minute. The blood pressure was 110/80 in the right arm and 108/76 in the left arm. Examination of the head, eyes, ears, nose, and throat revealed no abnormalities. There were a few râles at the base of the right lung posteriorly. The apex beat of the heart was 10 cm. to the left of the midsternal line in the sixth intercostal space. The base of the heart was enlarged to percussion, measuring 10 cm. transversely. The heart sounds were regular, rapid, and well heard. There were no murmurs, shocks, or thrills. The abdomen and extremities appeared normal. Because of the poor

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condition of the patient, the neurologic examination was limited. However, the deep reflexes were normal, and no abnormal reflexes were elicited.

The patient was given $\frac{1}{6}$ grain of morphine sulfate and $\frac{1}{200}$ grain of atropine sulfate hypodermically. In a few minutes the patient became dyspneic, and started to cough and expectorate greenish-black mucus. At 8:15 A.M., he became restless, thrashed about, gasped violently for air, became very pale, and was soon pulseless. In spite of stimulants, the patient died at 8:30 on the morning of admission.

Post-mortem examination was performed by one of us (J. Z.) two hours after death.

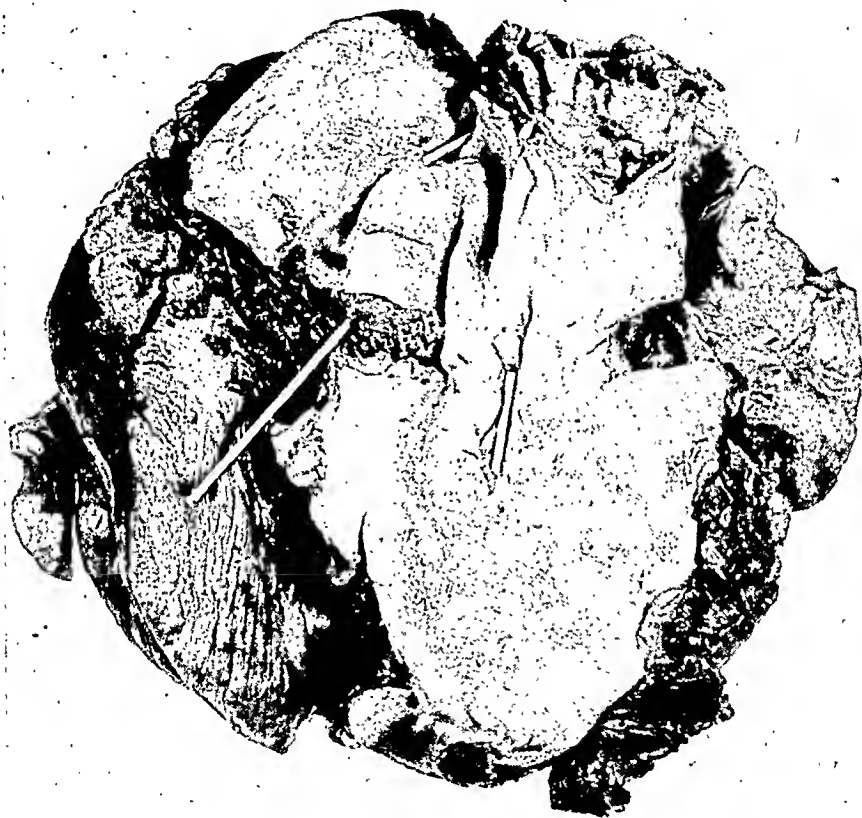


Fig. 1.—View of the descending thoracic aorta. The lungs lie at both sides of the opened vessel. The uppermost indicator is coming out of the coarcted area. Note the appearance of an obstructing band at this point. The left lower indicator points to the area of fatal, terminal rupture. The right lower indicator lies in a deep tear in the intima. Note the presence of numerous other rents in the intima. However, none of these invade the media. There was no evidence of any inflammatory process in any portion of the vessel.

POST-MORTEM OBSERVATIONS

The body was that of a well-developed white man, 25 years of age. External examination revealed only extreme pallor of the mucous membranes.

The left pleural cavity contained about 4,000 c.c. of blood and blood clot. The right pleural cavity was normal. The posterior mediastinum and the upper portion of the retroperitoneal area of the abdominal cavity contained clotted blood. The pericardial cavity contained no blood or serous fluid.

The heart weighed 410 grams. The muscular tone was good. The left ventricular wall measured 15 to 19 mm. in thickness. The right ventricular wall averaged 3 mm. in thickness. The ventricular cavities appeared normal. The auricular appendages contained no thrombi. All of the valves and coronary vessels were normal. The aortic valve showed no spreading of the commissural angles and no thickening of its free margins. The ascending aorta and transverse portion of the arch were normal in diameter and appearance. At the junction of the transverse with the descending thoracic aorta, there was a constriction of the lumen, as if by a fibrous band. The diameter of the lumen at this portion was 7 mm. From this point caudad, the lumen was markedly increased in size, measuring 20 mm. in circumference at its widest portion. The dilatation had a fusiform appearance. It extended for a distance of 15 cm., almost reaching the diaphragm. Opening the vessel disclosed a transverse rent in the wall 3 cm. in length at the midportion. This was the source of the bleeding. There were numerous other tears of the intima, but these were not deep (Fig. 1). The abdominal aorta was normal. The branches of the thoracic aorta proximal to the obstruction were slightly dilated, but no erosion of the under surfaces of the ribs was seen.

The left lung showed only compression atelectasis. The right lung was congested. All the other organs appeared normal, except for marked pallor.

Microscopic examination of the coarctation showed an excessive amount of fibrous tissue beneath the intima. There was no evidence of any active inflammatory process. Sections from the aneurysm revealed no signs of syphilis or atherosclerosis. The media showed patchy areas of mucinous degeneration. The intima appeared normal. There was some thickening of the subintima.

COMMENT

The coarctation was at the point where the ductus arteriosus meets the aorta. During obliteration of the ductus there must have been an extension of the fibrotic process into the aorta. This appears to have been the case because microscopic examination of the stenotic area showed only fibrous tissue beneath the intima. In the case reported by Hecker,² the coarctation was in the same location. The sequence of events in the formation of the aneurysm is more difficult to understand. It may be that the eddy formation just distal to the constriction resulted in a weakening of the aortic wall and a gradual dilatation of the lumen. This was progressive over a period of years. Eventually, because of some excessive strain (coughing), there was a sudden increase in the pressure within the sac, with rupture of the weakened wall. The presence of numerous tears in the intima, in addition to the ruptured area, suggests that there must have been a rather sudden increase in pressure within the aneurysm.

SUMMARY

1. Aneurysm of the aorta distal to a coarctation is uncommon.
2. A case which occurred in a 25-year-old white man is presented.
3. A possible explanation for the anatomic abnormalities is offered.

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CHRONIC OCCLUSIVE ARTERIAL DISEASE
(ARTERIOSCLEROSIS OBLITERANS), ASSOCIATED
WITH RETINITIS PIGMENTOSA

CASE REPORT

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RETINITIS PIGMENTOSA is apparently a vascular disease of the retina which is rarely associated with generalized peripheral vascular disease. A search of the literature concerning peripheral vascular disease associated with retinitis pigmentosa revealed only one article.¹ The scarcity of this pathologic combination makes the following case of interest.

Since the discovery of the ophthalmoscope the cause of retinitis pigmentosa has been disputed. Among the numerous theories of its causation that have been advanced are toxic or endocrine factors, trauma from light, and avitaminosis. It is not the purpose of this report to discuss the etiology, but to point out that whatever the process, whether it be one of localized susceptibility, choroidal sclerosis, or endogenous influences, the vascular changes may be of a general and peripheral nature, rather than just localized in the retinas.

CASE REPORT

J. R. P., a railroad brakeman, aged 56 years, married and the father of two healthy children, was first seen in July, 1942. His mother died at 45 years of age from puerperal sepsis; his father died at 91 years of age. He had six siblings, one of whom was known to show no evidence of retinitis pigmentosa. The patient could give no family history of this condition. His past history was negative except for influenza in 1917 and an accident which had occurred two years before. He knocked a fragment from his left knee cap and fractured his left elbow and some ribs. His leg was in a cast for three weeks, and it was after this cast was removed that he first noticed the left leg becoming smaller. For years he had smoked one or two packages of cigarettes daily and used alcohol occasionally.

His chief complaints were of pain in his left leg and exhaustion. These first appeared during the latter part of the previous winter. He noticed coldness of his left foot. If he would put his foot on a locomotive fire box, he could keep it warm. Both legs cramped after exercise, but the left one was always worse. It seemed strange to him when warmer weather came that his foot continued to be so cold and his leg tired so easily. A week previous to admission he had been mowing the lawn for an hour, when he developed a sharp pain in his left leg and a cramp in its calf. Rest and massage gave relief. When he tried to

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From the Caylor-Nickel Clinic, Bluffton, Ind.

push the mower again, he was able to go only 50 feet before the pain and cramp returned. After ten minutes he was at ease. At rest he suffered no pain. Walking only half a square precipitated the pain. He had lost 13 pounds in the preceding year and noticed considerable exhaustion for six months. Otherwise, his history was essentially negative.

Physical examination revealed a 56-year-old man, 129 pounds in weight and 67 inches in height. His mouth was edentulous, with only an upper plate. The eye grounds were described by the ophthalmologist⁶ as typical of retinitis pigmentosa. The patient's heart sounds were distant. The blood pressure was 125/80. The ulnar pulsations were diminished on both sides. Neither the dorsalis pedis nor the posterior tibial pulse was palpable on the left. The left foot was much paler than the right, and the left lower extremity appeared definitely smaller than the right. The femoral pulsations were equal and of good quality.

TABLE I
LEG MEASUREMENTS ON JULY 13, 1942.

SITE	LEFT (INCHES)	RIGHT (INCHES)
6 inches above patella	14 $\frac{3}{4}$	16 $\frac{3}{4}$
6 inches below patella	12 $\frac{1}{4}$	12 $\frac{7}{8}$
Lower extremity	36 $\frac{1}{2}$	37

Table I shows that the left lower extremity was definitely smaller than the right, especially above the knee.

TABLE II
OSCELLOMETRIC INDICES ON JULY 13, 1943

SITE	LEFT	RIGHT
Popliteal	1	2 $\frac{1}{2}$
Anterior tibial	0	3

The oscillometric indices listed in Table II show absence of the deep circulation in the area supplied by the anterior tibial artery of the left leg.

TABLE III
SKIN TEMPERATURES, MEASURED WITH A GENERAL ELECTRIC THERMOCOUPLE ON JULY 13, 1942

SITE	LEFT (DEGREES)	RIGHT (DEGREES)
Ball of foot	84 $\frac{1}{2}$	84 $\frac{1}{2}$
Dorsum of foot	89 $\frac{1}{2}$	91 $\frac{1}{2}$
Mid-calf	89 $\frac{1}{2}$	91 $\frac{1}{2}$
Mid-thigh	94 $\frac{1}{2}$	95

The skin temperatures listed in Table III reveal that the left lower extremity was not completely adjusted to a deficiency of the deep circulation.

The hemoglobin was 15 Gm., the erythrocyte count, 5.36 million, and the leucocyte count, 9,200, with a fairly normal differential count. The

⁶H. Brooks Smith, M.D.

Mazzini flocculation test was negative, the blood urea nitrogen, 16.3 mg. per cent, and blood sugar, 80 mg. per cent. Urinalysis was negative, and the basal metabolic rate was +9 per cent. The prostatic secretion contained a few pus cells, and culture revealed gram-positive cocci in pairs and tetrads.

Dental roentgenograms revealed no disease. The electrocardiogram and chest roentgenogram showed nothing abnormal. Roentgenograms of the lower extremity from above the knee to, and including, the foot showed no definite areas of calcification. There was one small area of calcification just below the head of the fibula and between the tibia and fibula which might have been in the anterior tibial artery.

SUMMARY

A case of retinitis pigmentosa, associated with chronic, occlusive, peripheral vascular disease, is presented. Although the cause of retinitis pigmentosa is still disputed, this case suggests that the pathologic changes in the retinae may not be localized there, but may occur as a part of a similar disorder elsewhere in the body.

REFERENCE

1. Brown, W. M., and Whitney, E. L.: Peripheral Vascular Picture in Retinitis Pigmentosa, *Arch. Ophth.* 24: 984, 1940.

Abstracts and Reviews

Selected Abstracts

Keys, A., Stapp, J. P., and Violante, A.: Responses in Size, Output and Efficiency of the Human Heart to Acute Alteration in the Composition of Inspired Air. *Am. J. Physiol.* 138: 763, 1943.

The results are reported from numerous experiments in which acute hypoxia was produced in twenty-seven normal young men. All studies were made under constant environmental conditions with the exception of the partial pressures of the gases in the inspired air. In most cases the pO_2 corresponded to that at 18,000 to 28,000 feet altitude; in some cases CO_2 at 14 to 30 mm. Hg was present. Some experiments were made with inspiration of pure oxygen. Exposure lasted from 10 to 48 minutes.

From roentgenkymographic measurements it is concluded that cardiac dilatation does not take place under these conditions. The stroke volume remains nearly constant in this acute hypoxia and the minute output of the heart is increased only slightly more than in proportion to the pulse rate change. Cardiac efficiency is unimpaired.

Carbon dioxide increases the altitude tolerance, and in hypoxia with CO_2 added the pulse rate increases less than without it. Again, the heart does not dilate and the stroke volume tends to remain constant.

Respiration of oxygen at four to five times the normal pO_2 results in a slight decrease in cardiac "work" and "effort" with no significant change in heart size or efficiency.

Blood pressure responses have no certain predictive value as to whether syncope is to occur. In the present series complete syncope occurred in ten cases. There is always a relative bradycardia in recovery from hypoxic syncope.

Indications were seen that acute hypoxia disturbs the stability of the autonomic nervous system.

It is concluded that, in normal young men, attempts to strengthen or safeguard the heart under hypoxic conditions would serve no useful purpose. The heart does not seem to be the limiting factor in tolerance to acute hypoxia.

AUTHORS.

Marcuse, F. L., and Moore, A. U.: Low Heart Rate in the Newborn Rat. *Am. J. Physiol.* 139: 49, 1943.

One-day-old rats, when compared with 120-day-old (tamed) rats, were found to have a significantly lower heart rate and less fluctuation in heart rate. Sex differences present in the tamed, mature animals were not present in the 1-day-old animals.

In the first 24 hours of life significant changes in heart rate were observed. In a twenty-one-day period of daily heart recordings, it was observed that heart rate increased steadily in the first 11 days of life; a plateau of no increase in rate prevails from the eleventh to twenty-first days; sex differences manifest themselves with increasing clarity from the tenth day on.

AUTHORS.

Wiggers, H. C., Glaser, G. H., Canavarro, K. de S., and Treat, A. E.: Arterial and Central Venous Pressure Changes Following Complete Transection of the Spinal Cord (C₈-T₁). *Am. J. Physiol.* 139: 217, 1943.

This study concerns the acute arterial hypotension and associated phenomena which occur following transection of the spinal cord (CS) of supine lightly anesthetized cats. When the transection procedures were uncomplicated by severe hemorrhage, pressures did not descend to critical levels. The hypotension developed after the skeletal musculature of the thorax, abdomen, and hind limbs, which supposedly support the elastic postarterial vessels, had been rendered completely flaccid. Apparently, however, the venous return of these supine animals was not impaired by the loss of this extravascular support. The criteria for this concept are based upon the fact that atrial and effective venous pressures were, if anything, slightly elevated, while the heart rates remained tachycardic. The slopes of the ascending limbs of arterial pressure pulses revealed no changes indicative of an impaired stroke output.

In explaining the equivalent decrease of systolic and diastolic pressures on a hemodynamic basis, it was deduced that reduction of peripheral resistance is a major contributing factor, but that some additional dynamic event must be involved. The analysis suggests that an increase in the capacity of the aorta and its immediate large branches is involved. The acute hypotension following spinal transection may be considered to result from an increase in the capacity of and a reduction in resistance to blood flow throughout the entire arterial system from the root of the aorta to the capillaries. There is no evidence to support the postulate that an impairment of skeletal muscle tone or the extravascular mechanism is herein concerned with the fall in blood pressure in these supine animals.

AUTHORS.

Boyer, P. K., and Bailey, C. V.: Concentration of Carbon Dioxide in Expired Air in Heart Disease. *Arch. Int. Med.* 71: 529, 1943.

In man, regardless of age, sex, basal metabolism, or state of nutrition, the concentration of carbon dioxide in the expired air is strikingly constant.

Measurement of the concentration of carbon dioxide in the expired air during the determination of basal metabolism by the open circuit method is a valuable clinical aid in the study of the cardiac status and of the effectiveness of therapeutic measures; it is especially helpful in classifying patients with cardiac disease complicated by hyperthyroidism and obesity, in whom dyspnea on exertion is difficult to interpret; it is unique among methods of estimating cardiac function in that it is performed with the patient at rest; it measures the extent to which respiration compensates for circulatory failure.

AUTHORS.

Gubner, R., and Ungerleider, H. E.: Electrocardiographic Criteria of Left Ventricular Hypertrophy: Factors Determining the Evolution of the Electrocardiographic Patterns in Hypertrophy and Bundle Branch Block. *Arch. Int. Med.* 72: 196, 1943.

An electrocardiographic diagnosis of left ventricular hypertrophy can be made before advanced changes have occurred. Employing criteria established by a study of a large number of normal subjects and persons with hypertension, the authors found that the electrocardiogram is a valuable device for detecting left ventricular hypertrophy and is somewhat more sensitive than the teleoroentgenogram. The electrocardiographic and roentgen changes do not necessarily parallel

one another, and at times either may be relatively normal while the other shows definite evidence of hypertrophy.

Left ventricular hypertrophy may be considered to be present when left axis deviation occurs in association with any of the following changes:

1. Increase in amplitude of the QRS complex, best expressed by the sum of R_1 and S_6 . Hypertrophy is present if this sum exceeds 2.5 millivolts and is probably present if it is over 2.2 millivolts. The increase in voltage is the earliest electrocardiographic change in hypertrophy.

2. Any perceptible depression of the S-T segment in Lead I, even of as slight a degree as 0.5 mm. (0.05 millivolt).

3. Lowering of T_1 below 1 mm., or further degrees of abnormality of T_1 .

The changes in the S-T segment and the T wave may develop in the absence of left axis deviation, and left axis deviation is not an unvariable or necessarily integral part of the electrocardiographic pattern of left ventricular hypertrophy. It is shown that the usual occurrence of left axis deviation with left ventricular hypertrophy in hypertension is due largely to predominant obesity with transverse position of the heart, which in itself causes left axis deviation. In slender subjects with left ventricular hypertrophy, left axis deviation is not so often observed.

The increased amplitude of the QRS complex may most reasonably be attributed directly to an increased mass of left ventricular musculature. The changes in the S-T segment and the T wave are regarded as due to relative ischemia of the deeper layers of the left ventricle. This is occasioned by increased work of the heart without commensurate increase in coronary flow. Several factors, which are discussed, contribute to cause this disproportion.

The particular vulnerability of the subendocardial region of the left ventricle is due to an intramyocardial pressure gradient during contraction. During systole there is a marked increase in intramyocardial pressure in the deeper layers of the left ventricle, which exceeds aortic pressure and which obstructs coronary flow in this region, although there is no interference in coronary flow in the outer zone of the left ventricle or in the right ventricle or auricles, where the intramyocardial pressure does not rise above the arterial pressure. The subendocardial region of the septum and the left ventricle on this account is the area most vulnerable to ischemia. It is the site of predilection of myocardial disease when there is a relative insufficiency of coronary flow, as in hypertrophy, or when there is an absolute decrease in flow, as in coronary artery sclerosis and acute coronary artery occlusion.

Over a long period, the chronic subendocardial ischemia leads to irreversible changes, and replacement fibrosis occurs. This involves the Purkinje distribution network of the left bundle branch which ramifies in the subendocardial region of the interventricular septum and the left ventricle. Interference with left ventricular excitation caused by diffuse involvement of the conduction system leads to slurring, notching, and widening of the QRS complex, eventually progressing to the pattern of left bundle branch block, which is frequently encountered in association with long-standing and advanced left ventricular enlargement. The widening of the QRS complex is only in slight part attributable directly to increased thickness of the left ventricular myocardium.

Changes in the S-T segment and the T wave in Leads II and III, and, ultimately, right bundle branch block, occur in conditions associated with chronic right ventricular strain, such as pulmonary stenosis, cor pulmonale, and long-standing mitral disease. The pathogenesis of these changes, just as in left ventricular hypertrophy, is similarly related to ischemia of the subendocardial region of the right ventricle consequent to increased intraventricular pressure in the right ventricle.

Gardberg, M., and Ashman, R.: *The QRS Complex of the Electrocardiogram.* Arch. Int. Med. 72: 210, 1943.

An analysis is presented of the QRS complex of the human electrocardiogram and of the variations in that complex which would appear when the heart is rotated to different positions within the thorax. Among different subjects there are considerable differences in the cardiac position within the thorax, and the effects of these differences are explained. In making the analysis, the authors have correlated experimental findings in the experimental animal, known effects of rotations of the heart in man produced by normal procedures or certain pathologic conditions, known effects of bundle branch block and of infarction in man, and information derived from studies of precordial leads. Less attention was given to the conflicting anatomic studies of the Purkinje system. In order to visualize the electrical events in three-dimensional space, clay models have been used.

The authors are convinced that, in a large majority of subjects, the directions of the electrical axes as revealed by the limb leads as projected on the frontal plane are correct within plus-minus 10 degrees, and the usual error may be less than this. It is pointed out that even if the error should be greater, the value of vector analysis is not thereby impaired in its more important applications.

AUTHORS.

Ungerleider, H. E., and Gubner, R.: *Extrasystoles and the Mechanism of Palpitation.* Tr. Am. Therap. Soc. 41: 1942.

An analysis was made of 1,142 cases with extrasystoles in order to determine their clinical significance. In 58 per cent no objective evidence of heart disease was found.

Ventricular extrasystoles occur with considerable greater frequency than supraventricular premature contractions, and in the presence of heart disease there is still greater preponderance of ventricular premature contractions.

Several factors, which are discussed, increase the significance of premature beats. Among these are: the occurrence of premature beats of multifocal origin; frequent and persistent premature beats, particularly if they occur successively in short runs interrupting the regular rhythm; a definite increase in the number or shower of extrasystoles immediately following exercise; occurrence of premature contractions in the presence of a rapid heart rate; inversion of the T wave in the regular beat which follows the extrasystole; and postextrasystolic pulsus alternans.

Palpitation is a very common symptom often associated with extrasystoles. It has been generally attributed to an increased forcefulness of the regular beat following the premature systole, but several reasons are presented which indicate that this explanation is not tenable. It is suggested that palpitation occurring with premature contractions or tachycardia is due to, or associated with, an increased intensity of the first heart sound resulting from a more forcible closure of the atrioventricular valves. The symptom of palpitation is of no particular significance and occurs in normal subjects as well as in those with heart disease.

AUTHORS.

Solarz, S. D., and Eleek, S. R.: *U-Wave Patterns in the Abnormal Electrocardiogram.* J. Lab. & Clin. Med. 28: 936, 1943.

In 1,000 cases with diagnostic electrocardiographic patterns, 94 cases of abnormal U waves were found. The U-wave patterns in these 94 cases showed the following chief characteristics:

a. In the left heart strain and in intraventricular block of the common type, the U-wave abnormalities consist of inverted U waves in Leads II and CF₄.

b. In the anterior wall infarction, abnormal (inverted or diphasic) U waves are found in Leads CF₂ and CF₄ with occasional similar abnormality in Lead I.

c. In posterior wall infarction, inverted U waves are found most commonly in Lead CF₄.

d. No abnormal U waves were found in right heart strain or in intraventricular block of the indeterminate S type.

A hitherto undescribed U-wave abnormality, a negative bowing of the T-P segment in Lead I, is discussed.

Instances of distortion of the T and P waves by large upright U waves and the confusion caused by the presence of prominent U waves in records of auricular fibrillation are pointed out.

Evidence is presented relating the presence of abnormal U waves to abnormalities of the S-T-T segment. In left heart strain and in the common type of intraventricular block, there is usually concordancy in the direction of the T wave, S-T deviation and U-wave direction. In posterior wall infarction there is concordancy of the deviation of the S-T segment and the direction of the U wave, but discordancy between T and U. In anterior wall infarction the reverse is true.

In serial records the abnormal U wave may undergo an evolution independent of the changes in the S-T-T segment.

AUTHORS.

Luisada, A. A.: On the Value of Mechanical and Acoustic Registration in the Diagnosis of Bundle Branch Block. *Rev. argent. de cardiol.* 9: 169, 1942.

A clinical case is described in which mitral insufficiency caused by rheumatic endocarditis was associated with arteriosclerotic heart disease. The electrocardiogram indicated a right bundle branch block. On the contrary, acoustic and mechanical records, as well as fluoroscopy, gave evidence of a delayed left ventricular systole.

A diffuse bilateral lesion of the myocardium is admitted. The "right side" type of the electrocardiogram is explained by the right ventricular hypertrophy caused by the valvular lesion, in spite of the predominance of myocardial lesions on the left side.

Considerations on the value of jugular vein tracings in the differential diagnosis between "opening snap" of the mitral valve and third heart sound follow.

A splitting of the C wave of the jugular tracing confirms the existence of two different components of this wave, each related to the activity of one ventricle.

AUTHOR.

Moia, B., and Battle, F. F.: The Electrocardiogram Before and After Exercise Following the Ingestion of Food. *Rev. argent. de cardiol.* 9: 339, 1943.

In thirty normal subjects, the electrocardiogram obtained within one hour after a common meal, before and after a standard exercise (climbing a sixty-step staircase), did not show any pathologic alterations.

In thirty patients suffering from typical or atypical attacks of angina pectoris, and with electrocardiograms which were normal or showed simple axis deviation but without signs of myocardial damage, the electrocardiograms, obtained at rest but within one hour after lunch, showed alterations characteristic of myocardial ischemia in 27.2 per cent of the cases.

After the ingestion of food, the performance of an exercise unable to provoke precordial discomfort (climbing at a moderate rate a 60-step staircase divided in three flights) gave positive results in 73.4 per cent of cases. The same exercise,

made several hours after lunch, produced definite electrocardiographic changes in only 23.3 per cent. In some of the patients in which this test was negative, the electrocardiographic changes appeared merely by eating.

The usefulness of obtaining electrocardiograms at rest or after a moderate exercise, within an hour of the ingestion of food, for the diagnosis of transitory myocardial ischemia, is emphasized.

The test is innocuous and produces no uncomfortableness.

The mechanisms by which the ingestion of food may originate or facilitate the appearance of the electrocardiographic changes described, are discussed.

AUTHORS.

Grier, G. W.: The Diagnosis of Congenital Heart Lesions in Children. *Am. J. Roentgenol.* 49: 366, 1943.

As regards roentgen diagnosis, congenital anomalies may be divided into three classifications:

A. Those with characteristic roentgen appearance.

B. Those in which the appearance is either not characteristic, or else similar in different lesions.

C. Those in which the roentgen appearance is either normal or abnormal, but offers no help in differentiating the lesion.

AUTHOR.

Fisher, C. E., and Mulligan, R. M.: Quantitative Study of Correlation Between Basophilic Degeneration of Myocardium and Atrophy of Thyroid Gland. *Arch. Path.* 36: 206, 1943.

A quantitative study has been made of basophilic degeneration of the myocardium in eight cases of atrophy of the thyroid gland, and in 142 control cases, of which 67 showed basophilic degeneration of the myocardium.

The number of muscle fibers affected by basophilic degeneration in an area of myocardium measuring 19.28 square millimeters was designated as the basophilic degeneration index (B. D. I.).

The basophilic degeneration index for the eight cases of atrophy of the thyroid gland was 40.5, and that for the eleven selected positive control cases was 7.7, showing a quantitative correlation between basophilic degeneration of the myocardium and atrophy of the thyroid gland.

AUTHORS.

Garvin, C. F.: Tricuspid Stenosis, Incidence and Diagnosis. *Arch. Int. Med.* 72: 104, 1943.

Of 119 consecutive patients who died of rheumatic heart disease and were examined post mortem, 43 (36.1 per cent) showed involvement of the tricuspid valve; in 13 of these the process had advanced to definite tricuspid stenosis (10.9 per cent of the 119 cases).

No new symptoms or signs helpful in diagnosis were discovered. The study did emphasize, however, the importance of chronic organic rheumatic tricuspid insufficiency as an indication that stenosis is likely, for in each one of the seven cases of organic tricuspid insufficiency included in the series there was more or less stenosis.

Three cases of tricuspid stenosis were diagnosed clinically. One of the patients had very severe tricuspid stenosis, the circumference of the orifice measuring 3.5 cm. Nevertheless, clinically there was pulsation of the jugular veins and of the liver. Apparently, marked stenosis of the tricuspid valve need not prevent the phenomena of tricuspid insufficiency.

AUTHOR.

Weiss, S., Stead, E. A., Jr., Warren, J. V., and Bailey, O. T.: Scleroderma Heart Disease With a Consideration of Certain Other Visceral Manifestations. *Arch. Int. Med.* 71: 749, 1943.

The clinical histories of nine patients with generalized scleroderma are reported. Post-mortem examinations were performed on two patients. These nine patients were selected for study because they all had symptoms and signs of heart disease. Both the clinical and the pathologic studies indicate that the sclerodermatous process is not confined to the skin but involves other organs. The cardiac failure is caused by myocardial scarring of an unusual type. Roentgen examinations may show involvement of the lungs. Dysphagia is common and esophageal stricture occurs.

These patients demonstrate that scleroderma heart disease is a clinical and pathologic entity.

AUTHORS.

La Due, John S.: Myxedema Heart: A Pathological and Therapeutic Study. *Ann. Int. Med.* 18: 332, 1943.

Hydropic vacuolization, loss of striation, branching, pyknotic nuclei and irregularity in staining properties of the muscle fibrils are seen in myxedema heart but are not specific for this entity.

Thiamin and vitamin B complex are ineffective therapeutic agents for myxedema heart.

AUTHOR.

Selye, H., Hall, C. E., and Rowley, E. M.: Malignant Hypertension Produced by Treatment With Desoxycorticosterone Acetate and Sodium Chloride. *Canad. M. A. J.* 49: 88, 1943.

The nephrosclerosis produced by desoxycorticosterone acetate overdosage in the rat is particularly pronounced if the animals are kept on a high sodium chloride intake. Under such conditions, desoxycorticosterone acetate causes a pronounced rise in systolic and diastolic blood pressure, marked diuresis with increased excretion of sodium and chloride, proteinuria and clinical signs of severe cardiac decompensation. In some instances death ensues, due to hemorrhagic lung edema.

The characteristic pathologic findings in rats so treated are hypertrophy and capsular fibrosis of the renal glomeruli with hyalinization of their tuft capillaries. Fibrosis, hyalinization, and even actual necrosis of the arteriolar walls is evident not only in the kidney itself, where the vasa afferentia are particularly affected, but also in the pancreas and the adrenal capsule. In the pancreas these vascular changes are frequently accompanied by edema and pronounced stroma proliferation. The experimental disease thus produced bears a striking resemblance to the hypertensive heart disease of renal origin as seen in man.

AUTHORS.

Grollman, A., Harrison, T. R., and Williams, J. R., Jr.: The Mechanism of Experimental Renal Hypertension in the Rat. The Relative Significance of Pressor and Anti-Pressor Factors. *Am. J. Physiol.* 139: 293, 1943.

Unilateral nephrectomy or the application of cloth or collodion to one kidney caused hypertension in a small percentage of normal rats. The subsequent removal from such animals of the kidney, to which cloth or collodion had been applied, did not result in a significant decline of the elevated blood pressure. Total

nephrectomy in animals surviving sufficiently long tended to cause an elevation of blood pressure. The bearing of these experiments on the theories of the pathogenesis of experimental renal hypertension is discussed.

AUTHORS.

Katz, Y. J., and Goldblatt, H.: Studies on Experimental Hypertension. XXI. The Purification of Renin. *J. Exper. Med.* 78: 67, 1943.

Extraction of finely ground fresh hog kidney with distilled water adjusted to pH 7.8 sodium hydroxide, followed by successive treatment, as described, with trichloroacetic acid and acetone, gives renin in good yield of a purity suitable for physiologic studies and a good starting material for further purification. It contains 15 dog units per milligram of nitrogen.

Further successive purification of this material with ethyl alcohol and ammonium sulfate gives a preparation containing 130 dog units per milligram of nitrogen. The purest preparation hitherto reported contained 16.0 to 20.8 units per milligram of nitrogen. Preliminary Tiselius electrophoresis studies suggest homogeneity, but further studies to establish purity are in progress.

The properties of the most purified renin indicate that it is a protein. Its chemical and physiologic properties correspond to those of the material in crude renal extract which induces an elevation of blood pressure when it is injected intravenously.

AUTHORS:

Richardson, G. O.: Atherosclerosis of the Main Renal Arteries in Essential Hypertension. *J. Path. & Bact.* 55: 33, 1943.

Of thirty-two cases of essential hypertension examined at autopsy, twenty-five showed the presence of atherosclerotic plaques in one or both main renal arteries, with varying grades of apparent stenosis.

Examination of 113 nonhypertensive controls showed plaques in eight cases. In only three of these were the lesions of comparable severity to those seen in the cases of essential hypertension.

These findings are discussed, and it is suggested that atheromatous plaques may be capable of producing renal ischemia and consequent hypertension analogous to experimental hypertension.

AUTHOR.

Page, I. H.: Hypotension and Loss of Pressor Response to Angiotonin as the Result of Trauma to the Central Nervous System and Severe Hemorrhage. *J. Exper. Med.* 78: 41, 1943.

Angiotonin refractoriness and hypotension follow upon injury to the central nervous system in dogs and cats. Refractoriness does not develop when the nervous system is quickly and expertly destroyed or the activity of the nervous system depressed by widespread injection into it of a local anesthetic. The syndrome develops in the absence of the kidneys and the suprarenal glands.

Glycine, methyl isothiurea, and rest are the only agents studied which tends to restore responsiveness, and the first two of these have only an irregular and temporary effect.

There is a marked degree of specificity in the syndrome since undiminished pressor responses to adrenalin, tyramine, and methyl isothiurea are observed during complete angiotonin refractoriness.

Despite the prolonged hypotension, change in the amount of plasma proteins and in the hematocrit readings is not striking.

Parallelism seems to exist between the fall in blood pressure after trauma to the nervous system and development of angiotonin refractoriness. After the syndrome has developed, elevation of the blood pressure by the injections of gum aencia solution or whole blood does not restore the responsiveness to angiotonin.

Angiotonin refractoriness and hypotension also develop after marked hemorrhage. Suprarenalectomy or nephrectomy does not prevent its appearance.

AUTHOR.

Logue, R. B.: Dissecting Aneurysm of the Aorta. *Am. J. M. Sc.* 206: 54, 1943.

A study of dissecting aneurysm of the aorta is presented. An ante-mortem diagnosis was made in ten of the twelve cases observed and confirmed on necropsy.

Isolated instances of dissecting aneurysm complicating calcareous aortic stenosis and syphilitic aortic insufficiency are presented. A new sign of this disease is described, consisting of a bruit and thrill over the femoral artery.

A history of previous hypertension, or an elevation of the blood pressure at the time of admission, was noted in eleven of the twelve cases.

Tamponade was the cause of death in seven cases. Hemorrhage into the pleural cavity, uremia, coronary occlusion, and ventricular fibrillation were the other causes of death.

AUTHOR.

English, J. P., and Willius, F. A.: Hemorrhagic Lesions of the Coronary Arteries. *Arch. Int. Med.* 71: 594, 1943.

Hemorrhagic lesions were observed in the walls of the coronary arteries in 54 of 135 hearts (40 per cent) and were directly or indirectly related to acute occlusion of the coronary artery in 20. The lesions were characterized by hemorrhage associated with the presence of large lipoid-containing cells, proliferative intimal changes, and organization. Smaller, less active lesions usually were found adjacent to encrusted plaques. The intimal changes that coexisted with the hemorrhage appeared to represent the primary factor in the pathologic condition; the hemorrhage was secondary. It does not seem logical, moreover, that hemorrhage in itself can have produced the effects observed.

AUTHORS.

Graef, I.: Medial Hypertrophy of the Renal Arterioles in Pregnancy. *Am. J. Path.* 19: 121, 1943.

A case is reported of chronic unilateral hematuria in a colored female, 29 years old, who was cured by nephrectomy during the fifth month of pregnancy. The removed kidney revealed unusual, massive, medial hyperplasia and hypertrophy of the arterioles. There was accompanying intimal fibromuscular hyperplasia of the interlobular branches of the renal artery. Focal fresh hemorrhagic erosions were found in the pelvis and ureter.

The medial hypertrophy could not be accounted for by any known or demonstrable injury. A hypothetical explanation is offered, based on the theory that hormonal activity during pregnancy might be responsible for changes in the arteriolar smooth muscle comparable to those found in the gravid uterus.

AUTHOR.

Holman, R. L.: Experimental Necrotizing Arteritis in Dogs. III. Bilateral Nephrectomy as Effective as Heavy Metal Injury in Its Production. *Am. J. Path.* 19: 147, 1943.

Acute necrotizing arterial lesions affecting principally the large elastic arteries (aorta, endocardium of the left auricle, pulmonary and coronary arteries) have been produced with regularity in dogs by combining three factors: maintenance on a standard low-protein diet, plasma alteration (usually repeated daily injections of plasma obtained from healthy donor dogs), and heavy metal injury, both uranium nitrate and mercuric chloride.

In the present report it has been shown that bilateral nephrectomy can be substituted for heavy metal injury, thus indicating that renal injury rather than heavy metal as such is the essential factor.

AUTHOR.

Wikle, H. T., and Cabot, N.: Embolectomy for Riding Embolus of Abdominal Aorta. *Surgery* 13: 264, 1943.

Although the patient died twenty-seven days postoperatively, from what was apparently pulmonary infarction, the authors feel that the case is of sufficient interest to be reported because it does prove again that patients with severe cardiac conditions can be subjected to major surgical procedures without immediate mortality.

Autopsy would have made the case complete, and it is to be regretted that such a report is not available. However, in summary, a case of riding embolus at the bifurcation of the aorta is reported; the patient withstood three major surgical procedures in spite of the fact that she had a severe cardiac condition; and technique of embolectomy has been illustrated.

AUTHORS.

Luke, J. C.: Retrograde Venography of the Deep Leg Veins. *Canad. M. A. J.* 49: 86, 1943.

A technique for performing retrograde femoral venography is described, and, in the course of twenty-nine such venograms, it has been found that the valvular mechanism of the femoral vein and its deep tributaries will allow retrograde flow of a contrast medium down the vein, even in cases of a normal leg. This is in contradistinction to the saphenous veins where the normal valve stations resist high pressure when retrograde injection is attempted. It is pointed out that retrograde venography is of use when a clear filling of the femoral vein is desired, and has its main indication in determining the presence or absence of a previous "silent" femoral phlebitis.

AUTHOR.

Bellis, C. J.: Measurement of the Circulation Rate: A Review of the Methods. *Surgery* 13: 27, 1943.

A brief historical review of the methods which have been used for the determination of the circulation rate has been presented. This information formed the basis for selecting sodium cyanide as the determinant in surgical patients. These results are described in a succeeding paper.

AUTHOR.

Bellis, C. J., Doss, A. K., and Craft, C. B.: The Circulation Rate After Operation, With Special Reference to the Effect of Position. *Surgery* 13: 35, 1943.

Usually, the cubital vein-to-carotid body time and ankle vein-to-carotid body time, as determined by the sodium cyanide method, is shortened after major surgery. In 191 cases, the average preoperative cubital vein-to-carotid and ankle vein-to-carotid body times were 17 and 36 seconds, respectively; postoperatively, the times were 14 and 32 seconds, respectively.

Circulation rates vary widely in patients with apparently normal circulatory systems.

Acceleration of blood flow postoperatively is probably related to the increased metabolic demands of the organism, which are manifest by increased temperature, pulse rate, and respiration.

Gravity retards the flow of blood from the upper and lower extremities, either when the position of the extremity itself is changed or when the longitudinal axis of the entire body is altered.

Fowler's position delays the return of blood from the lower extremities.

Ankle vein-to-carotid body circulation rate is shortened by active motion of the foot or toes and by elevation of the extremity.

AUTHORS.

Stewart, H. J., Carty, J. R., and Seal, J. R.: Contributions of Roentgenology to the Diagnosis of Chronic Constrictive Pericarditis. *Am. J. Roentgenol.* 49: 349, 1943.

Roentgenologic study is of considerable importance in the differential diagnosis of chronic constrictive pericarditis.

When venous engorgement, serous effusions, and hepatomegaly are present, indicating obstruction to the flow of blood through the heart, the composite roentgenologic picture pointing most conclusively to chronic constrictive pericarditis as a cause of this obstruction is as follows: A small or only slightly enlarged heart of abnormal configuration and often a rim of calcium at the periphery. The aortic knob is absent or flattened and deformed. Roentgenoscopic examination reveals the excursions of the margins to be diminished to the point that the heart seems almost to be standing still. When the patient is tilted from side to side, the heart remains fixed in the midline and fails to elongate when the diaphragms move downward. Pulmonary congestion is usually evident, pleural thickening or effusion and extrapericardial adhesions deforming or imparting abnormal motion to the diaphragm may be found. The kymogram confirms the marked decrease in the amplitude of pulsation over the borders of the heart and of the aorta.

Roentgenoscopic signs in the order of their diagnostic importance are: (a) limitation of the lateral shift of the anatomical axis of the heart with descent of the diaphragm when the heart is not greatly enlarged and there is no marked limitation of diaphragmatic motion; (c) decrease in the amplitude of cardiac pulsations over portions or all of the cardiac silhouette; and (d) paradoxical motion or deformity of the diaphragms due to the tugging of adhesions.

Calcification is the most reliable sign of chronic constrictive pericarditis, especially when the cardiac silhouette is enlarged, but is present in less than half of the cases and, when present, does not always indicate constriction of the heart. It is sometimes visible under the roentgenoscope but is best demonstrated in lateral roentgenograms, and, occasionally, heavy exposures are necessary to demonstrate its presence.

In the absence of calcification, the most common roentgenographic signs of chronic constrictive pericarditis are: (a) a small and flattened or absent aortic knob; (b) abnormal configuration of the cardiac silhouette, usually with a tri-

angular or globular shape and loss of the normal subdivisions of the borders; and (c) evidence of pulmonary congestion.

The size of the cardiac silhouette, when small, is of considerable importance, but a marked increase in size or evidence of cardiovascular disease of other etiology (hypertension and arteriosclerosis, for example) does not necessarily rule out the diagnosis of chronic constrictive pericarditis. In these cases the diagnosis is more difficult but can usually be made from the composite roentgenologic and clinical pictures.

There was no constant relationship between the thickness of the pericardium removed at operation and the size of the cardiac silhouette in roentgenograms.

The roentgen kymogram is of considerable aid in the diagnosis, especially in the study of the pulsations along the aorta and right border of the heart where the amplitude of pulsation was found to be most regularly reduced. In addition to the reduced amplitude of pulsation, flattening and irregularity of the diastolic peak of the wave is sometimes a helpful but less important finding. Pulsations of normal or greater than normal amplitude may be seen over portions or all of the left border.

No constant changes in the size or appearance of the cardiac silhouette or of the aorta were observed following operation. Some hearts became larger, others smaller. Increase in the amplitude of pulsations in the kymogram were regularly seen over portions or over all the cardiac silhouette but could not be related to the degree of relief afforded by pericardiectomy.

AUTHORS.

Sagall, E. L., Horn, C. D., and Riseman, J. E. F.: Studies on the Action of Quinidine in Man. I. Measurement of the Speed and Duration of the Effect Following Oral and Intramuscular Administration. *Arch. Int. Med.* 71: 460, 1943.

After the administration of a cinchona derivative to a human being, the electrocardiogram uniformly shows an increase in the time from the beginning of the Q to the end of the T wave. In the present study, this index of the effect of the human heart was used to measure the speed and duration of action of quinidine and quinine administered to human beings either orally or by intramuscular injection.

The effect became evident shortly after the administration of a single dose by mouth, reached a maximum in one and one-half to three hours, was then maintained at a slightly lower degree for three to five hours, after which it decreased, at first rapidly, then more slowly, and was no longer evident in twenty-four hours.

Quinine was much less effective than quinidine.

Larger doses of quinidine sulfate did not change the time of the maximum response, although the effect became evident sooner and was more prolonged.

The response to intramuscular administration of injectable quinidine (a solution of quinidine hydrochloride with urea and antipyrine) was much more prompt (within fifteen minutes) and the magnitude of effect was slightly greater, but the duration of effect was approximately the same as when an equivalent dose was given by mouth.

When doses are given repeatedly either orally or intramuscularly, the response at any moment is essentially the sum of the separate effects of the individual doses acting at that moment.

These results indicate that, in the treatment of acute arrhythmias, the administration of quinidine should be repeated at intervals of two to two and one-half hours. This permits observation of the maximum effect of the preceding dose before continuation of therapy with minimum loss of time.

If more rapid control of the rate is required, administration of the drug may be repeated at intervals of one hour until the desired degree of slowing is attained, after which, therapy can be continued at intervals of two to two and one-half hours.

In the treatment of acute arrhythmias, intramuscular administration should provide more constant and earlier response and eliminate the uncertainties and irregular absorption of oral medication. Intravenous administration is unnecessary and unwise.

AUTHORS.

Chavez, I.: Comparative Value of Digitalis and of Ouabain in the Treatment of Heart Failure. Arch. Int. Med. 72: 168, 1943.

In the face of the divergence of opinion about the value of ouabain in the treatment of heart failure, the comparative actions of digitalis and of ouabain are outlined and the results of twenty years' experience in the use of ouabain are set forth.

Digitalis and ouabain have similar, but not identical, action on the decompensated heart. By way of comparison, digitalis exerts a more pronounced effect on the functions of sinus excitation and atrioventricular conduction, which it depresses; ouabain, on the contrary, acts primarily on contractility and tonicity, which it stimulates.

Comparatively speaking, digitalis directs its chief effect on the differentiated, neuromuscular tissue of the heart; ouabain, on the undifferentiated, contractile fibers of the myocardium.

Digitalis, administered by the oral route, fixes itself slowly on the heart; ouabain, administered intravenously, acts with rapidity. The maximum effect of digitalis is reached in two or three days, whereas that of ouabain is reached in one or two hours. Digitalis accumulates; ouabain does not. On discontinuing the drug, digitalis extends its effects over a period of several days, up to eight or ten; those of ouabain disappear in twenty-four to thirty-six hours.

The best fields for the application of digitalis are: congestive heart failure with tachycardia and, especially, with auricular fibrillation; fibrillation even in the absence of heart failure; and long sustaining treatment of patients with slightly decompensated cardiac disease.

The best fields for the application of ouabain are the acute phenomena of failure of the left ventricle and chronic failure of the left side of patients with vascular disease, such as coronary arteriosclerosis, hypertension, and syphilitic aortitis.

The author recommends, as the best technique for the use of ouabain, one intravenous injection daily of 0.25 mg. in a series of six doses, and more, according to the tolerance of the individual patient and the clinical improvement obtained. In thousands of patients treated over a period of twenty years, the author has not encountered a single case of death attributable to ouabain.

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KERSHBAUM.

Peery, T. M.: Incomplete Rupture of the Aorta. *Arch. Int. Med.* 70: 689, 1942.

Small tears in the intima and media of the aorta are not uncommon findings at autopsy in cases of hypertension. These tears are thought to be an early stage of dissecting aneurysm, the stage before actual dissection has occurred. Most of the tears encountered have been transverse and across one of the commissures of the aortic valve. Tears in this area may result in slipping downward of the commissures so that the three valve cusps do not approximate, resulting in the clinical manifestations of aortic insufficiency. In some cases the tears heal at this stage, resulting in crippling of the aortic valve and death from congestive heart failure. In other cases dissection may occur days or months later, through the base of the old tear, and obliterate the evidence of a stage of incomplete rupture. In several instances reconstruction of the past history of a case of dissecting aneurysm has revealed two stages. The original period of substernal pain and sudden dyspnea or choking probably corresponds to the stage of actual dissection. If the tear occurs higher in the aorta, so that there is no effect upon the commissures, there may be no aortic insufficiency, and clinical manifestations may be slight. Occasionally a rough, rasping systolic murmur is noted over the aortic area. In cases in which dissection is preceded by incomplete rupture, the actual dissection is usually short, with termination by hemopericardium and cardiac tamponade. Of the eleven cases reported, five have shown incomplete aortic tears as purely incidental autopsy findings; two have died of congestive heart failure due to aortic insufficiency; and four have later developed dissecting aneurysm which resulted in death.

AUTHOR.

Bergman, A., and Neuman, J.: Thromboarteriosclerosis and Venous Thrombosis. *Medicina, Buenos Aires* 3: 87, 1942.

The clinical diagnosis of thromboarteriosclerosis does not presuppose the anatomical finding of an arterial thrombus or embolus.

The thromboses of the deep veins can aggravate the clinical picture of ischemia and lead to the amputation of a limb.

AUTHORS.

Ershler, I., Kossmann, C. E., and White, M. S.: Venous Pressure and Circulation Time During Acute Progressive Anoxia in Man. *Am. J. Physiol.* 138: 593, 1943.

In nineteen young, healthy, male subjects, acute progressive anoxia, induced by rebreathing, had the following effects:

The venous pressure showed a variable response. In four subjects it progressively decreased. In seven subjects, who fainted during the rebreathing, the venous pressure rose precipitously just before syncope, suggesting failure of the right ventricle. In all cases the venous pressure was restored promptly to normal by permitting the subject to breathe room air.

The circulation time from the right arm to the tongue was decreased in all subjects. This decrease was statistically significant. The rate of circulation was normal or slightly slower in some cases as soon as the oxygen saturation of the blood was restored to the control level.

AUTHORS.

Naide, M.: Treatment of Leg Ulcers With Blood and Concentrated Plasma. *Am. J. M. Sc.* 205: 489, 1943.

A simple method has been described for the treatment of ischemic and varicose leg ulcers with patient's own blood and with concentrated plasma. Nine of fifteen ulcers, refractory to other treatment, were healed, two were improved, and four failed to heal. This treatment results in rapid relief of pain and subsidence of the local inflammatory reaction.

AUTHOR.

Weston, R. E., Janota, M., Levinson, S. O., and Necheles, H.: Studies on Hemoconcentration and Shock Following Severe Hemorrhage. *Am. J. Physiol.* 138: 450, 1943.

Typical shock has been reproduced by graded hemorrhage in eleven non-dehydrated, and in fifteen dehydrated, unanesthetized, normal dogs.

In two of the nondehydrated (18 per cent), and in eight of the dehydrated animals (53 per cent), hemoconcentration occurred. Plasma volume and plasma protein determinations, before and after hemorrhage, revealed that the animals which hemoconcentrated actually lost additional plasma fluid and protein as shock developed.

Pathologic changes consisting of gastrointestinal engorgement and hemorrhage, pulmonary congestion and engorgement, and occasional changes in other viscera were observed in a number of animals.

The hemodiluting, nondehydrated animals tolerated an average total blood loss of 49 per cent as compared to an average total blood loss of 43 per cent tolerated by the other animals.

The changes in plasma protein concentration after hemorrhage indicated that the hemoconcentrating dehydrated animals hemodiluted during and after hemorrhage to a lesser degree than the other three groups. This relative inability to hemodilute could explain their inability to tolerate as much bleeding before going into shock, and could lessen the masking by earlier hemodilution of the subsequent hemoconcentration as shock develops.

It is suggested that the conflicting reports as to the occurrence of hemoconcentration after hemorrhage may be related to the state of hydration of the animals studied.

It is concluded that there are no definite grounds for differentiating between hemorrhagic shock and shock from other causes.

AUTHORS.

Fox, T. T., Travell, J., and Molofsky, L.: Action of Digitalis on Conduction in the Syndrome of Short PR Interval and Prolonged QRS Complex. *Arch. Int. Med.* 71: 206, 1943.

A case is reported in which the electrocardiographic picture of short P-R interval in association with prolongation of the QRS complex was exhibited. Observations were made over a period of nearly two years.

The effect of changes in vagal activity produced in various ways was studied.

The effect of atropine sulfate on this syndrome was always to shorten the QRS time. This indicates that there was a vagal component in the mechanism of the syndrome.

In repeated experiments digitalis uniformly produced widening of the abnormal QRS complex. That this effect involves vagal function was demonstrated by its disappearance after administration of atropine.

The results of this study are in harmony with the hypothesis that this syndrome is due to an aberrant conduction mechanism joining the sino node with one of the ventricles. According to this hypothesis, the widening of the QRS complex by digitalis is due, not to an action of the drug on intraventricular conduction, but rather to depression of the auriculoventricular node, resulting in increased activity of the aberrant auricular conduction tissue with consequent increased asynchrony of the ventricular responses.

AUTHORS.

Erratum

Fig. 1 of the article by William Dressler, "Myocardial Infarction Indicated by an Electrocardiographic Pattern in Which T_1 is Lower Than T_2 ," page 314, September, 1943, issue of the *JOURNAL*, was printed upside down. It is reprinted below in its proper position.

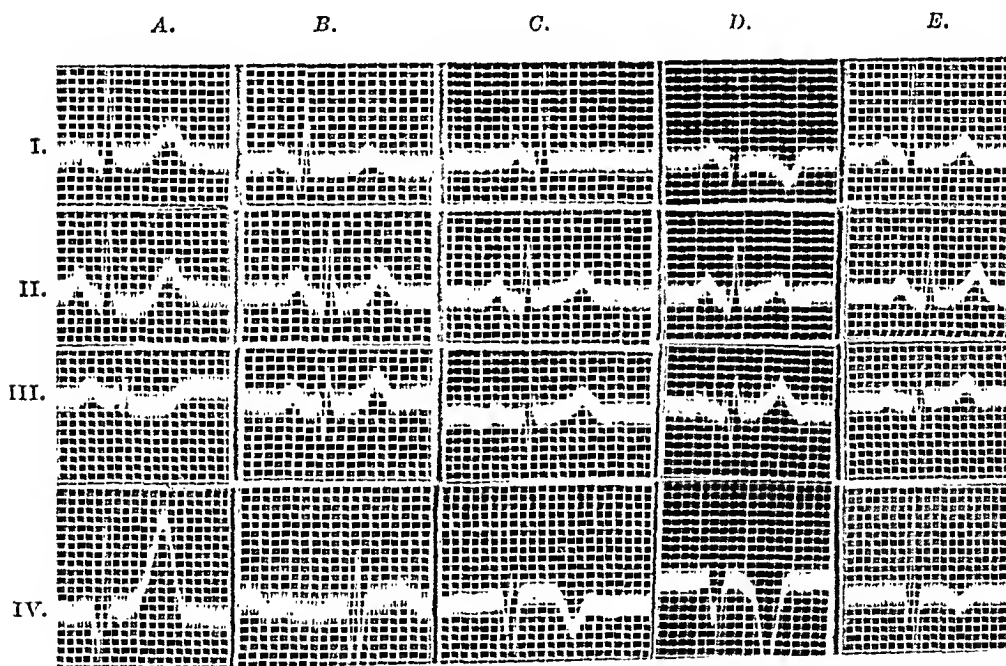


Fig. 1.—Case 1. A, Three hours after a severe anginal attack. The S-T segment is depressed in Leads II and III, and there is no corresponding elevation in Lead I. T_3 is nearly isoelectric. There is a deep Q wave and a high T wave in Lead IV.

B, Thirteen hours after the attack. The depression of the S-T segment in Leads II and III has subsided. T_1 has become flatter, and T_2 upright, resulting in the pattern $T_1 < T_2$. A W-shaped QRS complex is visible in Lead IV, and T_4 is of low voltage.

C, Five days after the attack. The S-T segment in Lead I is slightly convex, and a dip has appeared at the end of T_1 . There is sharp inversion of T_4 .

D, Five weeks after the attack. T_1 is inverted and there is a marked increase in the voltage of the negative T_4 .

E, Four and a half months after the attack. T_1 has become positive again. The inverted T_4 has decreased in voltage.

Book Reviews

ROENTGENOLOGY OF THE HEART: Prepared by Robert M. Daley, M.D., Richard S. Gubner, M.D., and Harry E. Ungerleider, M.D., for the Medical Department of the Equitable Life Assurance Society of the United States. Published by the Picker X-Ray Corporation for free distribution, 1943, 19 pages, many illustrations.

This brochure deals with techniques for measurement of heart size and interpretation of the teleoroentgenogram, points out the practical applications of the kymogram, outlines the criteria for enlargement of the various heart chambers, and presents in very clear and concise fashion the significance of cardiac enlargement in the common types of heart disease. A bibliography of the more important contributions to the subject of cardiac roentgenology is appended.

For the most part, the material presented represents the consensus of investigators in this field. It contains a few statements concerning which one might hold an honest difference of opinion, depending upon one's training and experience. For example, on page 4, the authors recommend three views in the routine roentgenographic study of the cardiovascular shadow, the posteroanterior and the two obliques. In the experience of the reviewer, the lateral view should be included routinely, and usually either the left or right anterior oblique is sufficient in any given case, depending upon the type of cardiac disease which is present. In persons of middle age or beyond, the left anterior oblique view is desirable for visualizing the entire thoracic aorta, whereas, in children and young adults, the right anterior oblique view is the more important because of the likelihood of mitral valve disease and congenital lesions. The authors are to be commended for encouraging the use of the mid-clavicular line rather than the nipple line as a reference for the location of the apex impulse, but it should be pointed out that "the leftmost point at which a definite forward impulse is imparted to the palpating finger" is not as accurate as the point of maximum impulse for locating the actual cardiac apex. Extensive studies in which the heart borders have been projected orthodiascopically to the anterior chest wall have shown that the point of maximum impulse corresponds much more closely to the anatomic apex. The statement that "The electrocardiogram is the most sensitive method to detect left ventricular hypertrophy" is open to question. In the experience of the reviewer, the electrocardiographic pattern commonly known as "left ventricular strain" (Barnes) is likely to be a late manifestation, and frequently does not appear until long after ventricular enlargement is demonstrable by roentgenologic examination. It is true, however, that in the occasional case of so-called "concentric hypertrophy," the electrocardiographic pattern may be characteristic when no enlargement can be detected by measurement of the cardiac shadow.

Under the heading "Interpretation of the Teleoroentgenogram," the brochure calls attention to some very important points that are not generally recognized. For example, marked changes in the size of the heart shadow in a given person may result from deep inspiration or forced expiration, and only a teleoroentgenogram taken with the breath suspended in ordinary inspiration is suitable for heart size measurements. The pitfalls presented by the extrapericardial fat pad, the funnel chest, and scoliosis of the thoracic spine are well illustrated. Routine fluoroscopic examination, particularly in the lateral and oblique positions, tends to minimize the errors resulting from these complications.

In the opinion of the reviewer, the section on mensuration contains a really valuable contribution, namely, a relatively simple method of estimating the frontal area from measurements of the long and broad diameters, which was originally published by Ungerleider and Gubner in the AMERICAN HEART JOURNAL for October, 1942. Most cardiologists will admit, as emphasized by Ungerleider, that the cardiothoracic ratio is the poorest roentgenographic method of detecting cardiac enlargement, whereas orthodiascopic measurement of the frontal area of the cardiac silhouette is probably the most accurate. The latter has the obvious disadvantage of requiring a considerable amount of training in the technique. A teleoroentgenogram, on the other hand, can be taken in any laboratory by an ordinary technician. If the other disadvantages of measuring the frontal area, namely, the completing of the upper and lower borders and the use of a planimeter, could be obviated, one would have an ideal method for even the untrained. The method proposed by Ungerleider and Gubner approaches this ideal. They have shown that, by measuring the long and broad diameters of the frontal cardiac shadow and applying the formula for the area of an ellipse, the frontal area of the heart can be closely approximated without actually resorting to planimetry. This will be particularly welcome news to those who have found it impossible to obtain a planimeter because of war restrictions. The authors have constructed a nomogram from which the actual area can be estimated by simply laying a ruler across two scales and reading the frontal area on a third scale. The reviewer has applied this method to 155 of his own orthodiagrams in which the area had been measured by a planimeter. This group was made up of patients of all ages, and included normal hearts as well as the common types of heart disease in various stages. The calculated area corresponded exactly to the planimetric determination in 20 subjects (13 per cent), was slightly greater in 81 (52 per cent) and smaller in 54 (35 per cent). The calculated area exceeded the measured area by more than 5 per cent in 7 per cent of the cases, and dropped below minus 5 per cent in 2 per cent of the entire group. Using the measured area as a basis, the average amount by which the calculated area exceeded the planimetric area in the 81 cases was plus 3 per cent, and the average of the 54 cases which fell below the measured area was minus 2.5 per cent. This relatively close approximation to the planimetric area indicates that the method has a practical application of distinct value in the great majority of cases. The normal range probably should be increased by about 3 per cent to allow for the slightly decreased accuracy of the ellipsoid formula.

On page 9 of the brochure, the authors state that the broad diameter is *sometimes* drawn as the sum of two perpendiculars from the long diameter to the right and to the left heart borders. In the reviewer's experience, only the vertically placed heart permits the broad diameter to be drawn in one continuous line, and in *most* instances it has to be divided. Variation in the placing of the portion of the broad diameter which lies between the long diameter and the left border results in considerable difference in the calculated area. By trying several different points it was found that drawing it from the lower end of the left auricular salient (approximately 1.5 to 2 cm. below the junction of the left cardiac border and pulmonic arch) gave the most consistent results. The teleoroentgenogram illustrated in the brochure represents an ideal, but not the most common, type of cardiac silhouette. The nomogram is highly accurate, but would be much easier to use if the long and broad diameter scales were divided at every 0.2 cm. instead of every 0.5 cm. Its usefulness could be further enhanced by extending the frontal area scale in both directions.

The other methods listed for estimating heart size are probably of rather dubious value from a practical standpoint, and considerably less accurate than the method of Ungerleider and Gubner. What the authors refer to as the "aortic arch diameter" (sum of maximum extensions to the right and left borders of the vascular

pedicle from midline), on page 9, in reality represents the width of the great vessels, including the superior vena cava as well as the aorta. A more accurate method of measuring the diameter of the aortic arch is shown on page 10.

The criteria for the enlargement of the cardiac chambers are well presented. However, it should be emphasized that there is no accurate means of detecting enlargement of the right ventricle except by angiocardiography. The roentgenograms illustrating the changes in size and shape of the heart in various common types of heart disease are characteristic of the conditions represented.

On the whole, the brochure is well done, the material is authentic, and the illustrations have been carefully selected. It properly emphasizes the fact that measurement of cardiac enlargement has been lifted out of the realm of guesswork and has been made a procedure of mathematical precision. A simplified modification of the frontal area method of measuring heart size is presented, together with a nomogram for estimating the frontal area and a percentage deviation table which obviate the necessity for all computations. In the reviewer's limited experience with this "short cut," it is not quite as accurate as the planimeter, but, nevertheless, is highly practical.

CHESTER M. KURTZ.

HYPERTENSION: A MANUAL FOR PATIENTS WITH HIGH BLOOD PRESSURE: By Irvine H. Page, M.D., Director, Lilly Clinic, Indianapolis City Hospital. Charles C Thomas, Springfield, Ill., 1943, 69 pages, plus index, 7 illustrations, \$1.50.

The author, who is noted for his researches in the field of hypertension, has written a manual for laymen on the subject of hypertension. He has "attempted to give the patient an insight into his illness that he may be spared some of the dismay and alarm and avoid quackery that will assail him from every side." The author has "tried to explain" the purpose of various examinations given to persons with high blood pressure, what hypertension is, and what can be done about it. He has been eminently successful. That some of the explanations are somewhat complex for laymen does not detract from the value of the book; most of them are clear and precise. Perhaps the author could have condemned many proprietary remedies with advantage, but that would have made many patients unhappy with the treatment which they are receiving; the placebo effects of otherwise useless proprietary remedies may be substantial. The book is valuable not only for laymen for whom it was written, but for physicians for whom it was not written; many of them still maintain beliefs in old and scientifically disproved theories which are efficiently discarded in this volume. Almost all patients with hypertension and almost all doctors who treat patients with hypertension would benefit greatly from reading this manual. The book is highly recommended. In general it is a clear explanation of a puzzling and common disease which constitutes one of the greatest problems of modern life.

E. V. ALLEN.

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*Executive Committee.

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Original Communications

THE STRUCTURE AND INNERVATION OF THE CONDUCTIVE SYSTEM OF THE HEART OF THE DOG AND RHESUS MONKEY, AS SEEN WITH A SILVER IMPREGNATION TECHNIQUE

JOSÉ F. NONÍDEZ, Sc.D.
NEW YORK, N. Y.

THE present article is based on studies of serial sections of the heart impregnated with the Cajal silver nitrate technique. Since the presence of a differentiated conductive system in the dog has been questioned recently,¹ most of the work was carried out in this animal; the monkey was used chiefly for comparison and because it is more closely related to man. A correlation of some physiologic phenomena with the anatomic observations will be attempted in the discussion.

I. MATERIAL AND TECHNIQUE

The dog material consisted of the hearts of four puppies (1, 4, 7, and 40 days old, respectively), fixed with an alcoholic solution of chloral hydrate, followed by hardening in 95 per cent alcohol with a few drops of ammonia.* Before impregnation the hearts were divided into blocks; after reduction of the silver the blocks were dehydrated, embedded in paraffin, and cut serially; the plane of sectioning varied according to the structure to be studied. The best views of the conductive system were obtained in frontal sections, 12 to 14 μ thick. The material from the monkey consisted of the heart of a fully grown animal which was prepared in the same way except that a piece of the left ventricle was fixed with Bonin's fluid for routine staining.

The technique mentioned above does not impregnate all nerve fibers to the same degree. The axons of the sympathetic ganglion cells (sympathetic postganglionics) appear yellow to light orange, according to the length of impregnation; for this reason, namely, lack of contrast with the yellowish background of the preparation, they cannot be identified outside of the nerve bundles. All other nerve fibers, including the axons of the cells of the intrinsic cardiac ganglia (parasympathetic postganglionics), have greater affinity for the silver and

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*For further details of this technique see Nonidez.²

are stained dark brown to black.² The constancy of these differences, which have been verified experimentally for the sympathetic ganglia supplying the heart,³ makes it possible to follow the distribution of the parasympathetic axons, an advantage not possessed by other silver impregnation methods. In the adult monkey the contrast between the weak argyrophilia of the sympathetic axons and the greater affinity for the silver of the other nerve fibers is even more marked than in the dog, and is also conspicuous in the peripheral nerves.* This shows that the differences noted above are neither restricted to the visceral nerves nor influenced by age.

Although the technique used is primarily for impregnation of nerve cells and fibers, it permits identification of other tissues without counterstaining. Striated muscle fibers are well stained, and the capillaries are more readily identified than in sections prepared with routine procedures. The connective tissue fibers are not ordinarily impregnated, but, when they are, they stain so diffusely that they cannot be mistaken for nerve fibers. In the particular case of the heart, the Purkinje fibers are well seen because of their very light impregnation, in contrast with the ordinary myocardial fibers which stain more deeply (Fig. 9).

II. OBSERVATIONS

As far as the inferior (or distal) parts of the system are concerned, my observations on the dog corroborate the classical ones of Tawara.⁴ There is an atrioventricular node which is continued inferiorly into a main bundle (*crus commune*), and there are right and left bundle branches composed of Purkinje fibers. As will be shown presently, the node is richly supplied with nerve fibers, mostly axons of the ganglion cells of the subepicardial plexus, and this is in contrast with the inferior (distal) portion of the main bundle and right and left bundle branches and their ramifications, which are neither innervated directly by the vagus nor by the ganglion cells. Since the technique employed does not impregnate sufficiently the axons of the sympathetic ganglion cells, the problem of the sympathetic innervation of the conductive system is left unsolved. In addition to the atrioventricular node, there is a smaller sinoatrial node which is also supplied, although to a lesser extent, by parasympathetic nerve fibers.

The conductive system of the monkey follows the same plan as in the dog, but the main bundle and proximal portions of the right and left branches have numerous parasympathetic nerve endings. Typical Purkinje fibers are absent; instead there are fibers rich in sarcoplasm that resemble the transitional stages between the Purkinje elements and the ordinary myocardial fibers of the dog.

1. *The Sinoatrial Node.* a. *Structure.*—This node lies in the crista terminalis and consists of an elongated roundish mass (head) and a narrower portion (tail). It is best seen in very young puppies (Fig. 1, A). It has been described as a mass of irregularly anastomosed strands, separated by abundant connective tissue containing numerous

*The differential staining of the fibers in the peripheral nerves is very marked in preparations of the brachial plexus of an adult rhesus monkey.

capillaries.⁵ My observations on serial sections of the hearts of very young puppies do not agree entirely with this description. Indeed, in very young hearts, the trabeculated portion is actually the area of transition between the ordinary myocardium and the node proper. The latter has a more compact appearance, and consists of frequently anastomosed fibers of myoblastic aspect, with few myofibrils; their nuclei vary somewhat in size and are so closely placed in some areas that they almost touch each other (Fig. 2). Between the fibers there are slender capillaries and connective tissue which presumably increases in amount with age.

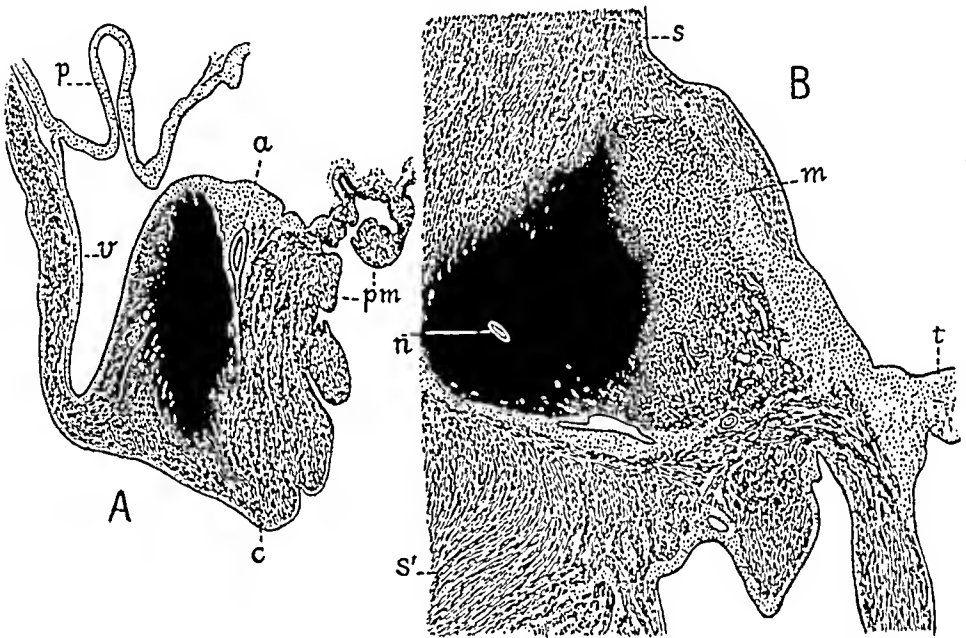


Fig. 1, A and B.—Camera lucida drawings showing the position of the sinoatrial and atrioventricular nodes, respectively, in a day-old puppy, drawn at the same magnification. Nodes, black. *a*, Artery supplying the crista terminalis, S-A node, and atrial wall; *c*, crista terminalis; *m*, main bundle (coarse stippling); *n*, nodal artery; *p*, pericardium; *pm*, pectinate muscles; *s*, *s'*, interatrial and interventricular septa, respectively; *t*, base of septal flap of the tricuspid valve; *v*, wall of the superior vena cava. Frontal series, posterior view of sections.

Irregular strands radiate from the node in every direction, but they are more numerous on its internal (mesial) aspect; many trabeculae invade the wall of the caval funnel, whereas others connect posteriorly with the muscular sheet that binds the atria together. As stated above, the strands or trabeculae represent the transition between the nodal tissue proper and the ordinary myocardium; accordingly, their fibers are richer in myofibrils and the nuclei are more scattered. Individual differences in the size and arrangement of the trabeculae may have led some authors to deny the existence of the node in adult hearts. Furthermore, the myoblastic fibers so clearly seen in the very young animal are capable of further differentiation with increasing age. On account of this, the S-A node of older puppies does not stand out as clearly as in the newborn, but careful study shows a lesser degree of

differentiation of its constituent fibers as compared with the ordinary myocardial elements. It is easy to understand, therefore, that to an observer who has not studied the heart of the newborn the differences noted may seem trivial.

The S-A node of the monkey occupies the same position as in the dog, but in the adult, at least, its fibers, although quite slender and wavy, contain more myofibrils, and their nuclei are somewhat more spaced. The trabeculated character of the node is more evident than in the puppy, and the spaces between the trabeculae contain larger amounts of connective tissue.

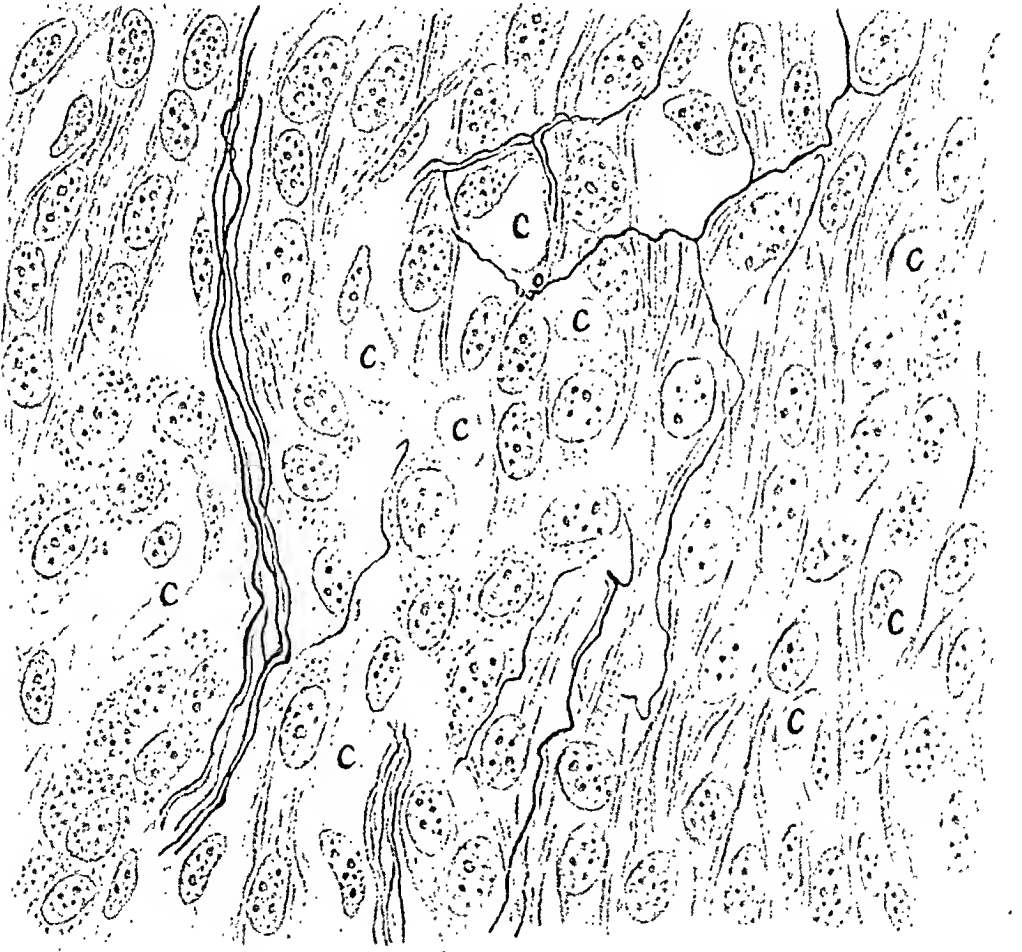


Fig. 2.—High-power drawing of a portion of the S-A node. Notice paucity and small diameter of the nerve fibers. The muscle fibers to the left of the figure approach the transitional stage, while those to the right are typical of the dense portion of the node. c, Capillaries.

b. Innervation.—The nerve supply to the S-A node is not as rich as might be expected, when one considers the wealth of nerve bundles in its vicinity. The bundles, as well as numerous ganglion cells, have been seen by several authors in diverse animals, mostly in routine slides; however, many of the nerve fibers in these bundles do not enter the node, but supply the ordinary myocardial fibers in the surrounding

region. The above statement refers only to the deeply impregnated parasympathetic postganglionics; the larger bundles also carry pale fibers (sympathetic postganglionics), but their final distribution could not be ascertained for reasons already mentioned.

With the technique used, the deeply stained nerve fibers to the node and juxta-nodal area can be traced to ganglia scattered in the extensive nerve plexus investing the caval funnel and extending under the epicardium of the intercaval space. Their distribution in the dog has been recorded by Bachmann,⁶ Schurawlew,⁷ and Nonidez.⁸ Small cells predominate in the ganglia of the caval funnel.⁸ The ganglion cells receive impulses through preganglionics coursing in the vagi. The existence of direct efferent vagal fibers is beyond experimental histologic demonstration because: (1) elimination of the axons of the ganglion cells would require destruction of all the ganglia in the vicinity of the node, and time should be allowed for degeneration of the axons (fourteen to twenty days); (2) even if the operation were successful, there would be left numbers of small afferent fibers which cannot be eliminated without section of the vagi, but this procedure would suppress at the same time the preganglionics and whatever direct efferent fibers may occur. Experimental evidence showing that the ganglion cells are the source of parasympathetic nerve fibers to the node is found in the work of Bachmann⁶ and Heinbecker and Bishop,⁹ and will be considered in the discussion.

The terminations of the parasympathetic postganglionics in the node do not differ from those previously described for the atrial musculature.² The finer branches end as minute single or double rings, "boutons," and small reticulated enlargements in contact with the surface of the muscle fibers. Swellings also occur along the twigs, and are probably as important for the discharge of stimuli as the terminal rings and enlargements. Nerve endings resembling the motor plates of skeletal muscle, as described by Blair and Davies,¹⁰ do not occur in the S-A node of the dog and monkey.

Afferent nerve endings are present in close proximity to the S-A node. They resemble the neuromuscular organs (muscle spindles) of skeletal muscles. In the monkey (Fig. 3) they are more elaborate than in the cat and dog, in which they were first noticed.⁸ These terminations are not numerous, and arise from thick myelinated fibers; their branches are wound around the muscle fibers of one or more bundles which run intramurally in the right atrium and are continuous with longitudinal muscle bundles in the wall of the superior vena cava. The finer branches of termination end as simple or double rings and lamellar enlargements of considerable size. Whether these perimuscular nerve endings belong to the conductive system is difficult to say. The constancy of their presence in the same position in the three species examined suggests that they function during some phase of

*Unpublished observations.

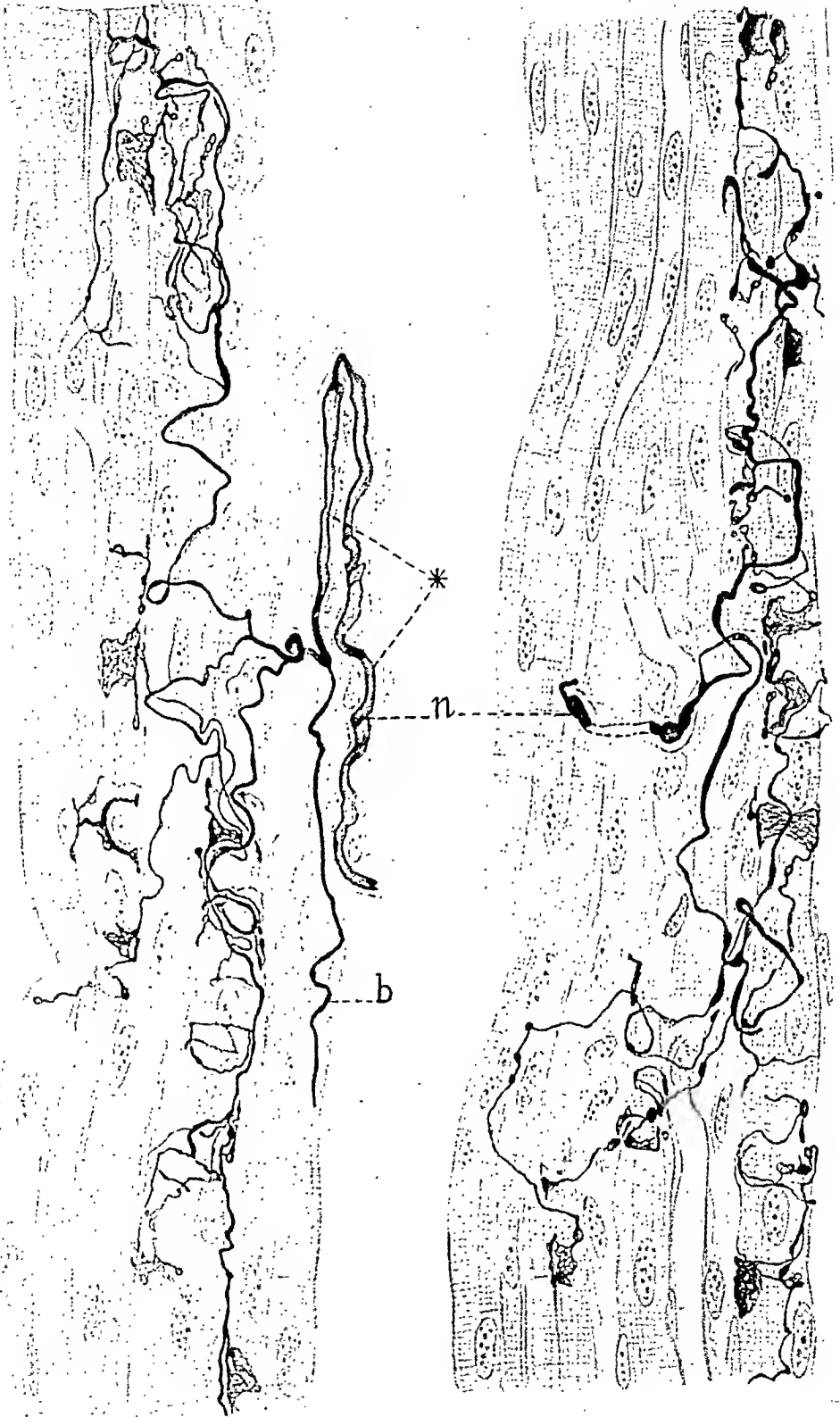


Fig. 3.—Perimysial nerve endings, heart of adult rhesus monkey. *n*, Nerve fibers. The portion * and branch *b* in the drawing at the left were copied from the section following the one represented.

the cardiac cycle, and the view has been advanced that they are the nerve endings for the hypertensive reflex of De Waele and Van de Velde (Nonidez¹¹). In the cat they persist after upper thoracic sympathectomy. In this animal, according to Pannier,¹² elaborate afferent nerve endings are also present in the nodal tissue, and similar terminations occur in the walls of the atria and auricles.

Meiklejohn¹³ has described, in the monkey, *Callithrix*, complex nerve endings wound around muscle fibers. According to this author, "Some of the more complex endings surround a cluster of nuclei which appear to be muscle nuclei, but which are much more closely grouped than the nuclei of the surrounding muscle." "Very closely resembling some of the more complex endings described above, are the networks occurring in the course of some of the fibers. A small fiber sometimes breaks up in its course into a complex network, showing varicosities at the terminations and in the course of the fibrils. . . . Such a network appears to be a 'station' on the course of the fiber: the one shown at Fig. 13 could be traced through five sections 7μ thick" (p. 8). From this description (based apparently on transverse sections of the heart) it appears that the elaborate endings described by Meiklejohn were in all probability transverse sections of clusters of branches of the extensive terminations represented in Fig. 3 of this article; they are best seen in longitudinal sections of the heart, in which their true shape is displayed.

In concluding the description of the innervation of the S-A node, it must be stated that, in the older animals which were examined, nerve fibers around and within the node were still scarcer than in the very young animals. This is undoubtedly due to spacing of the nerve fibers as a consequence of the growth of the myocardium. Accordingly, in serial sections of the adult heart it is difficult to visualize the extent of the innervation and the distribution of the nerve endings. It is for this reason that the hearts of newborn or very young animals were used in the present study.

2. *The Atrioventricular Node.*—The A-V node is larger than the S-A node and has a richer parasympathetic innervation.

a. *Structure.*—In the newborn puppy, portions of the node proper and the main bundle appear side by side in frontal sections of the heart (Fig. 1, B). The largest portion of poorly differentiated nodal tissue occurs internal to the bundle (*m*), with which it is connected through gradual transitions. The node consists of (1) fibers with a myoblastic aspect, namely, short spindle or slightly branched anastomosed cells, with few myofibrils and oval or elliptical nuclei (Fig. 4), and (2) larger cells with round nuclei and clear cytoplasm, with variable numbers of faintly argyrophilic granules. The latter cells also occur in the bundle, in which they tend to form rows; they gradually change into the typical Purkinje fibers characteristic of the more anterior (distal) portions of the bundle and its branches, to be described presently.

The more superior regions of the bundle and node (i.e., those portions nearest the opening of the coronary sinus) are not clearly defined because they are continuous with bundles of ordinary myocardial fibers. Of special mention is a bundle which passes toward the right side along the posterior wall of the root of the aorta, because it may be an important path for impulses reaching the node and main bundle from the left atrium.

The delimitation of the A-V node is still more difficult in the rhesus monkey. The loosely reticulated portion, which, according to most descriptions, should be regarded as the node (Fig. 7, *n*) is actually the zone of transition between the atrial myocardium and the nodal tissue, and is less profusely innervated than the more compact portion which is continuous with the main bundle. The elongated nodal portion shows anastomosed fibers of variable diameter, some of which are rich in sarcoplasm; the cross striations of their myofibrils are more conspicuous than in the puppy (Fig. 8).

b. Innervation.—Contrary to reports by other authors,^{10, 13} my observations on the A-V node clearly show that it has a richer innervation than the S-A node.* This discrepancy is probably due to the fact that the authors mentioned above used adult hearts, and also to the belief that the nerve bundles near the S-A node carry nerve fibers to this node, but in serial sections of the young heart it is evident that most nerve fibers in these bundles supply the atrial musculature, and that, as stated before, relatively few enter the S-A node proper. As to the use of adult hearts, it is to be remembered that the S-A node lies in the crista terminalis, where even in the adult it is easily accessible to the silver because of the thinness and relatively loose structure of the atrial wall, whereas the A-V node lies internally against the mass of dense connective tissue of the annuli fibrosi. Under such conditions the penetration of the silver in the region of the A-V nodes of adult hearts is more difficult than in the very young animal, in which the endocardium of the atrioventricular canal is much thinner than in the adult, and the connective tissue of the annuli less dense.

The parasympathetic nerve fibers ending in the node arise from ganglia located under the epicardium of the coronary sulcus and posterior atrial walls. Perinodal ganglia (present in the calf and sheep) are absent in the dog and monkey, but small groups of ganglion cells do occur within the interatrial septum in the vicinity of the node.

Fig. 4 gives an idea of the abundance of nerve branches and endings in the A-V node of the same (1-day-old) puppy from which Fig. 2 was taken. The nerve fibers and their branches form an elaborate plexus within the node. Reticulated swellings occur in the branches; in good

*Recent observations by E. W. Walls (Specialized Conducting Tissue in the Heart of the Golden Hamster [*Cricetus Auratus*], *J. Anat.* 76: 359, 1942) which appeared when the present article was ready for the press disclose a similar situation. According to this author, numerous nerve fibers could be traced into the substance of the A-V node; in contrast, the S-A node "has a poor nerve supply, no fibers or cells being demonstrable in the substance of the node."

impregnations the terminal rings and minute club-shaped terminal enlargements of the finer branches of the arborizations are clearly seen. In many instances the terminal rings and enlargements occur in contact with the myoblastic elements of the node.

The nerve fibers which branch within the node vary in diameter. When their relative thickness is taken into account, one is tempted to believe that the thicker fibers are afferent, but the type of their terminal arborization is not characteristic enough to permit a positive statement. Perimuseular endings of the type found in the vicinity of the S-A node (Fig. 3) do not occur in the region of the A-V node.

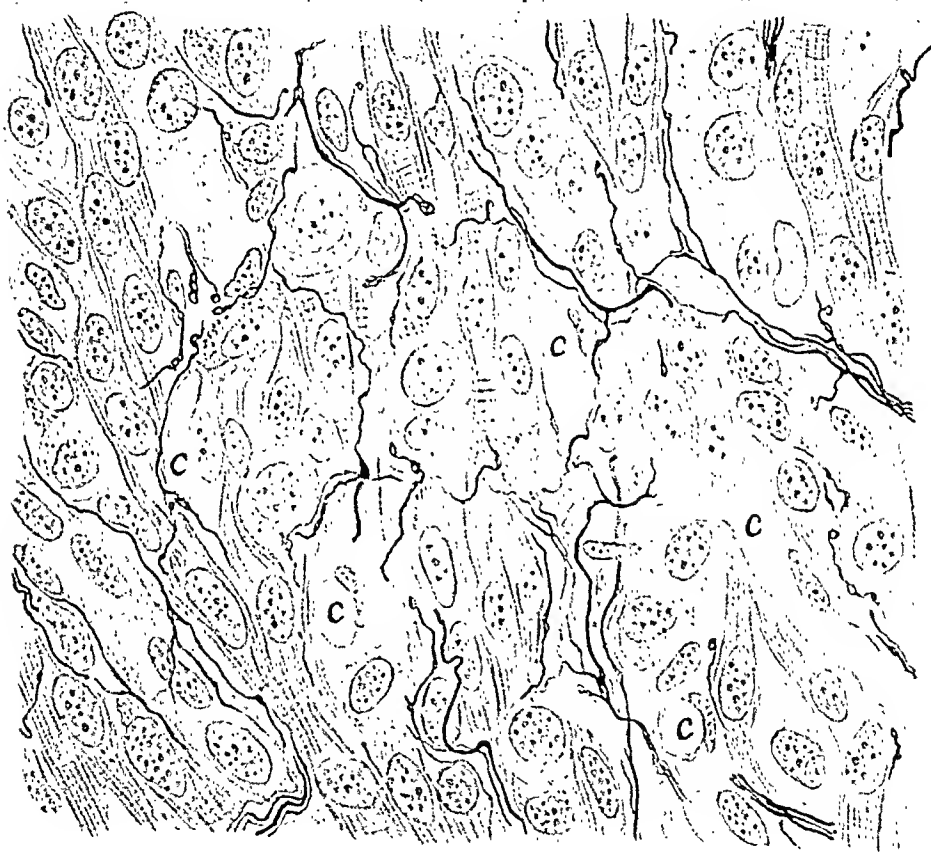


Fig. 4.—High-power drawing of a portion of the A-V node, showing nerve terminations. Same puppy as in Fig. 2, but slightly less magnified.

In the monkey the nerve fibers branch not only within the A-V node, but also in the main bundle and proximal portions of its two branches. The fibers divide repeatedly and end as in the dog. The trabeculated or intermediary portion has fewer nerve fibers and endings.

3. *The Main Bundle (Crus Commune).* a. *Structure.*—As already stated, the A-V node of the dog is continuous with a bundle composed of fibers identical with those described for the node, and, in addition, Purkinje fibers; the latter predominate in the inferior (or distal) half

of the bundle. In serial sections this bundle is seen to divide into right and left branches. As shown by Tawara, the main bundle runs in the midst of the narrow membranous portion of the septum. This is clearly seen in frontal sections of the heart. Fig. 5 is a camera lucida sketch of a section of the heart of a 40-day-old puppy, and shows the origin of the left bundle branch (b'). Since the series in this case begins posteriorly, the branch under consideration, running subendocardially on the left surface of the interventricular septum, appears

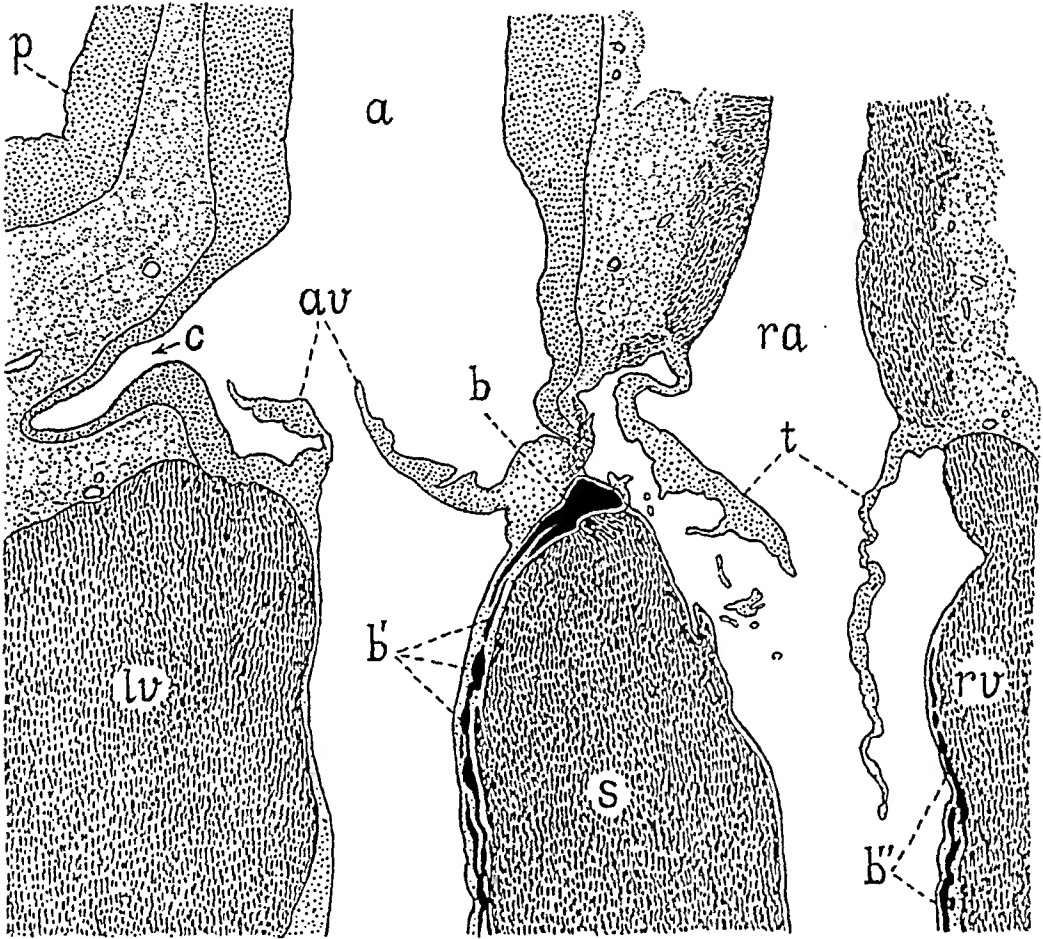


Fig. 5.—Camera lucida drawing showing the main bundle (b) in the membranous portion of the interventricular septum (s), the left bundle branch (b'), and the distal portion of the right bundle branch (b'') in the wall of the right ventricle (rv). a , Aorta; av , aortic valves; c , left coronary artery; lv , wall of left ventricle; p , wall of pulmonary artery; ra , right atrium; t , tricuspid valve. Posterior view of a frontal section of the heart, 40-day-old puppy.

toward the left of the figure. The right branch is not seen at this level because it is actually the continuation of the main bundle beyond the point of origin of the left branch; it divides into branches which continue distally within the septum and finally reach the surface of the right ventricle (rv), ascending subendocardially toward the atrioventricular orifice, in the vicinity of which they can still be detected (b''). The drawing is practically identical with Tawara's Fig. 7, Tafel I; the only difference is that the figure by this author was copied from a

series beginning anteriorly, i.e., the left branch appears toward the right of the observer.

Fig. 6 is a photomicrograph of the main bundle (*b*) in the same section from which the preceding figure was made. Even though it lacks detail, the contrast between the bundle (composed of Purkinje fibers) and the ordinary myocardial fibers of the interventricular septum (*s*) is quite marked. The presence of a space between the periphery of the bundle and the surrounding tissue is also evident.

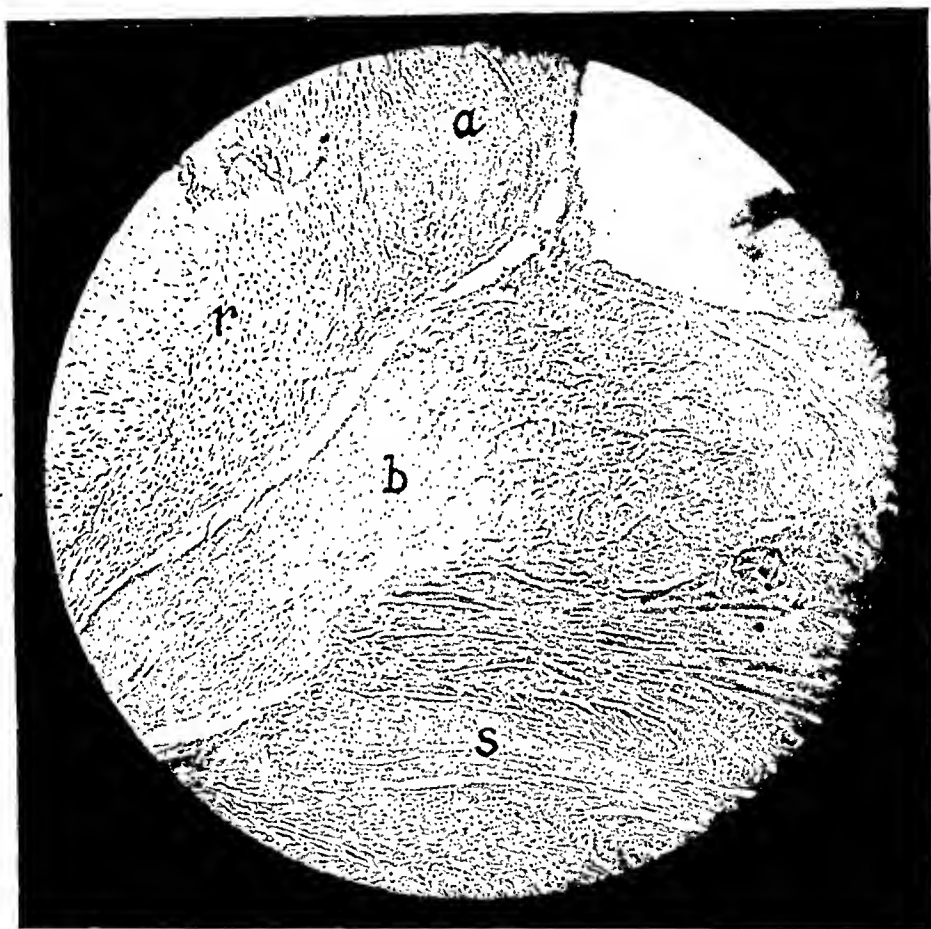


Fig. 6.—Photomicrograph of the main bundle (*b*) from section in the preceding figure. *a*, Atrial musculature; *r*, fibrous ring; *s*, musculature of the interventricular septum. Notice definite space between the bundle and the surrounding tissues.

Study of serial sections shows that, in this puppy, at least, the only connection between the atrial and the ventricular musculature is the main bundle. The existence of secondary connections in other puppies is within the bounds of possibility; if, as claimed by most investigators, the conductive system differs functionally from the ordinary cardiac musculature, it is questionable whether these connections would influence the physiologic properties of its tissue, but they may attenuate or even suppress the symptoms expected after block of the main bundle.

The above statements apply also to the monkey. Fig. 7 shows the A-V node and bundle (solid black) in the membranous portion of the septum (stippled). *A* shows the point of origin of the left branch (*b''*), while *B* shows also the right branch (*b'*). In contrast with the main bundle of the puppy, the corresponding structure of the monkey is more differentiated in the sense that the muscle fibers have more myofibrils and a correspondingly smaller amount of sarcoplasm; however, fibers with fewer myofibrils, a greater amount of sarcoplasm, and larger nuclei also occur in the bundle (Fig. 8).

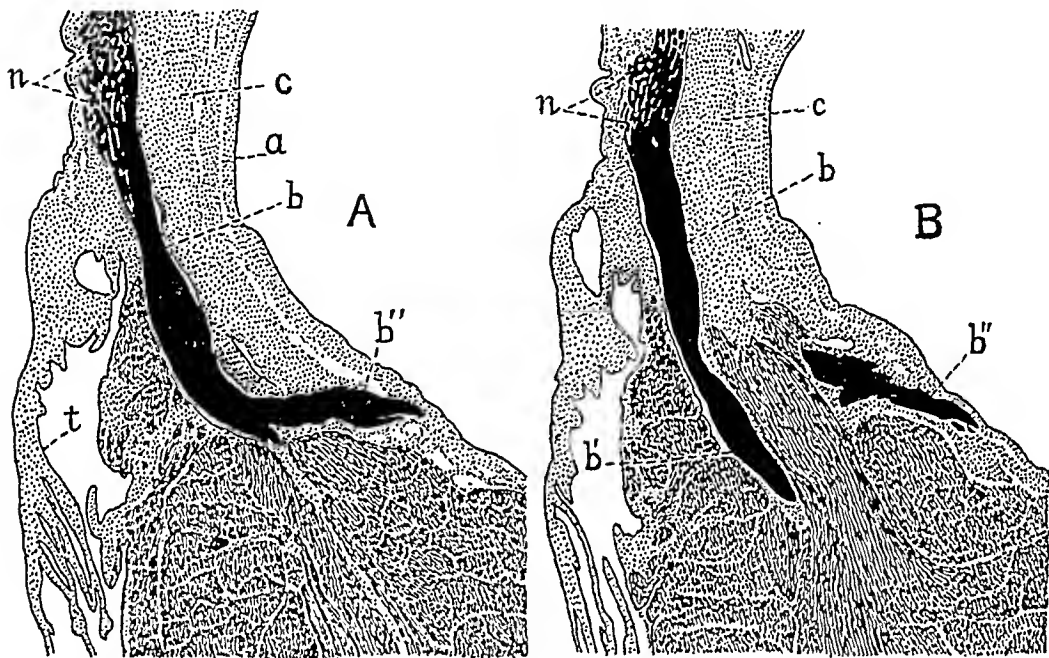


Fig. 7. *A* and *B*.—Camera lucida drawings of the A-V node, main bundle (*b*), and right (*b'*) and left (*b''*) bundle branches of an adult rhesus monkey. The space between the bundle and the surrounding tissues has been indicated. *a*, Wall of the root of the aorta; *c*, connective tissue of the pars membranacea of the interventricular septum; *n*, trabeculated portion of the A-V node; *t*, septal flap of the tricuspid valve. From a transverse series of the heart.

b. Innervation.—The extent of the parasympathetic innervation of the main bundle is different in the two animals studied. In the dog the nerve fibers are restricted to the superior part of the bundle (i.e., the portion next to the node) whereas in the monkey, as noted by Meiklejohn,¹³ nerve fibers and their arborizations occur throughout the bundle (Fig. 8) and course for some distance within the right and left branches, which they may reach through devious paths. It would seem, then, that crushing the A-V node and bundle in the monkey may not completely abolish the chronotropic effect of the vagus on the ventricular musculature, for numbers of nerve fibers from ganglia in the coronary sulcus may escape injury, whereas, in the dog, the operation suppresses vagal influence to the extent that in about 50 per cent of the cases it can be demonstrated only after eserine.¹⁴ The type of nerve endings that were found in the main bundle of the monkey is essentially the same as in the other portions of the conductive system.

4. *The Right and Left Bundle Branches and Their Ramifications.*—The structure of these branches differs in the two species studied. In the dog their component fibers resemble closely the Purkinje strands of the calf, sheep, etc., whereas, in the monkey, the differences between the Purkinje elements and the ordinary myocardial fibers are less marked.

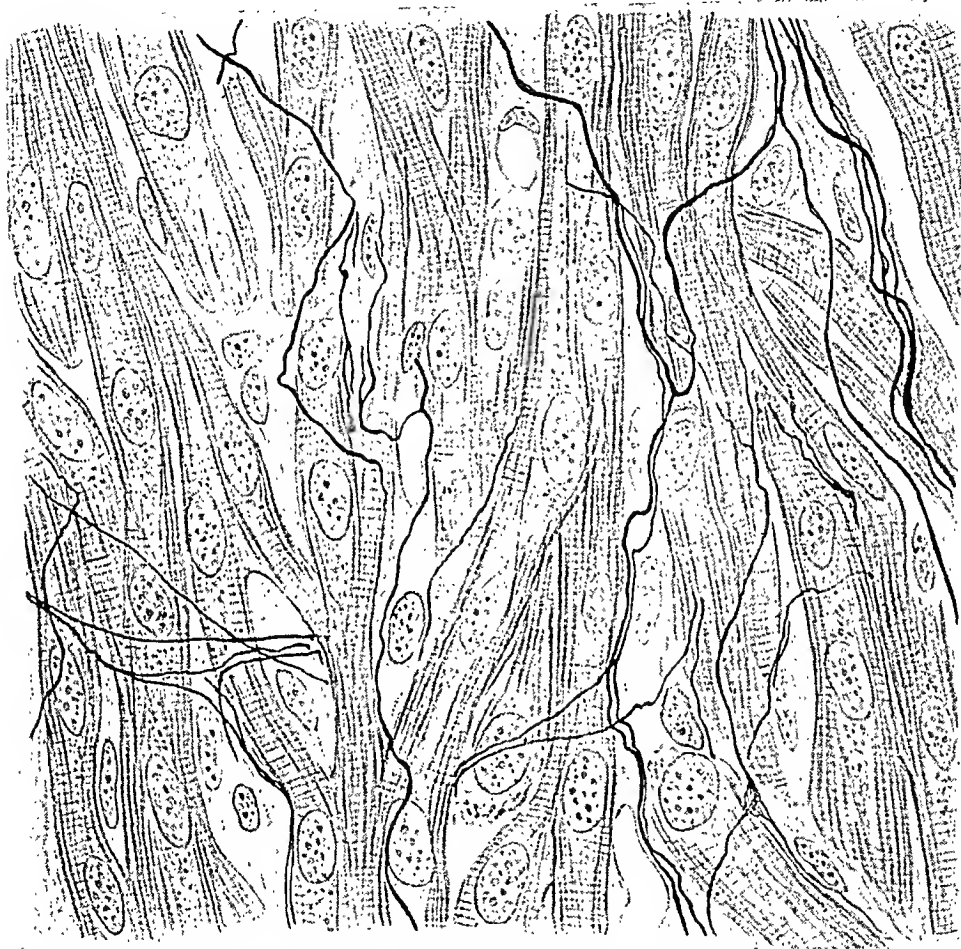


Fig. 8.—Nerve branches and terminals in the A-V bundle near the node, under high magnification. Same as in preceding figure.

a. Structure.—In the dog the branches divide repeatedly until an elaborate system of subendocardial strands is formed. The most typical Purkinje fibers occur immediately beneath the endocardium (Fig. 9, left). They have swollen portions which are separated from each other by constrictions. The swollen portions usually contain two nuclei which may be closely placed or separated; the nuclei often have a crescentic shape and may appear crenated. Distinct perinuclear spaces are seen in most segments. Each of the latter is crossed by myofibrils, gathered into definite bundles or running more or less independently.

The myofibrils of the different segments are continuous; as they pass through the constricted portion they show deeply stained granular enlargements, well illustrated by Tawara. Indeed, the Purkinje fibers in my preparations agree in every detail with those represented by this author in his Figs. 2, 3, and 5, Tafel V, taken from serial sections of the heart of a 3-day-old puppy. They also correspond to the elements labeled as Purkinje fibers in the photomicrographs published by Abramson and Margolin.¹⁵

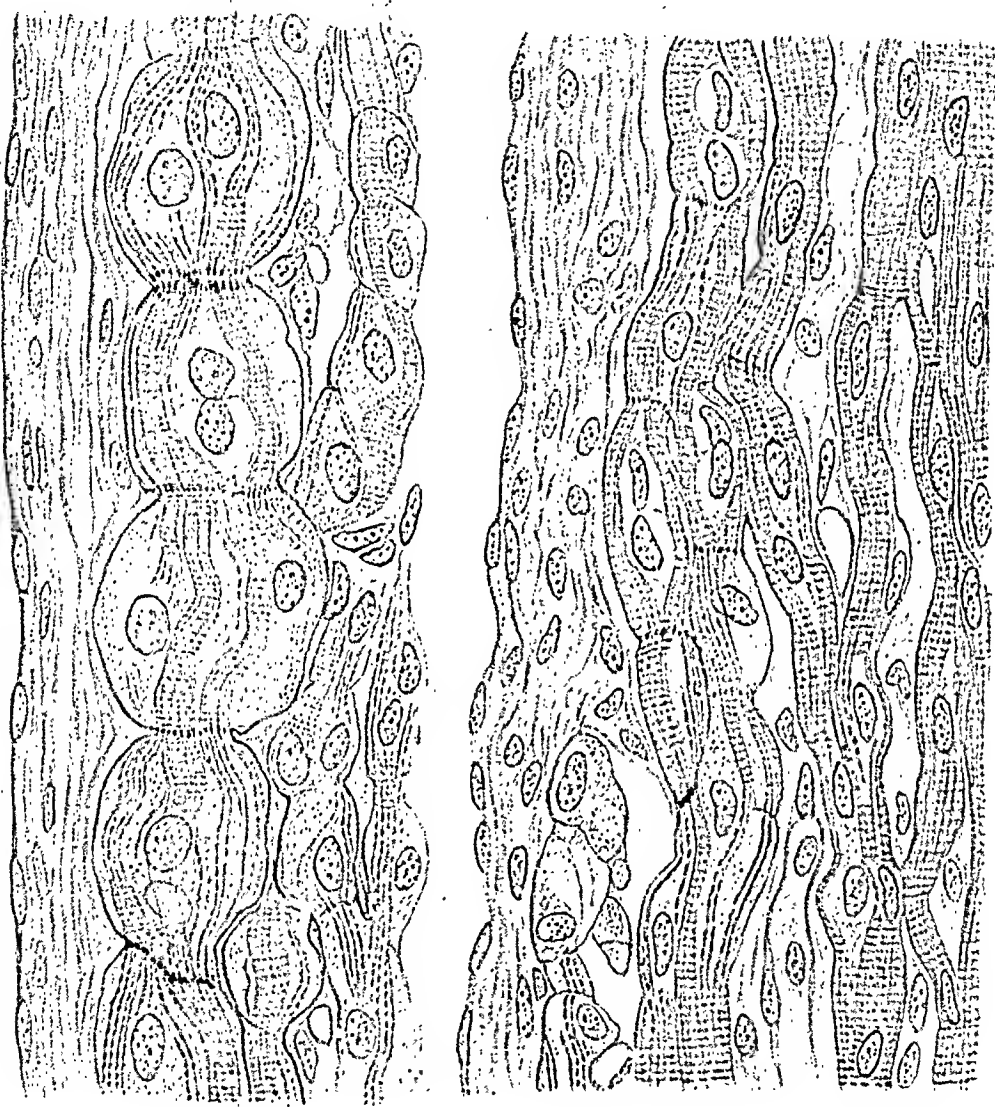


Fig. 9.—(Left) Subendocardial Purkinje fibers and (right) their transition into ordinary myocardial fibers. Notice absence of nerve fibers. Same puppy as in Figs. 5 and 6.

Immediately beneath the large Purkinje fibers there are strands composed of smaller segments containing one or two nuclei and fewer myofibrils (Fig. 9, left). These thinner fibers gradually connect with the ordinary cardiac fibers, either subendocardially or in the deeper

portions of the ventricular wall. The connection between the two types is better seen in the drawing at the right of the figure. Some of the slender segments have two closely placed nuclei of more or less crescentic shape, enclosed within a perinuclear space; the myofibrils seem more numerous and have thickenings as they pass from segment to segment of the fibers. These thickenings are not present in the ordinary cardiac fibers; the intercalated discs of the latter do not show in silver impregnations.

In the dog, at least, there can be little doubt that, although the Purkinje strands run predominantly parallel with the inner ventricular surface, they eventually connect with the myocardium. The term "embryonic," applied by Todd¹⁹ to the fibers rich in sarcoplasm and poor in myofibrils, is unfortunate because the muscle fibers of the atria and ventricles do not go through a stage corresponding structurally to the Purkinje fibers of postnatal life. Indeed, the formation of the Purkinje elements in the embryo is a process of gradual differentiation which is continued to some extent in early postnatal life.⁶ In newborn and very young puppies the Purkinje fibers are less distinct and thinner than in the older puppies.

The monkey lacks the typical Purkinje elements that are seen in the puppy, but the ramifications of the right and left bundle branches consist of fascicles which differ from the ordinary myocardial fibers. The Purkinje strands in this animal are composed of fibers of irregular size, embedded in connective tissue. Most fibers have a large amount of sarcoplasm which contains numerous spherical, closely placed, transparent granules appearing as rings in optical section; these granules do not occur in such an abundance in the ordinary cardiac muscle fibers. The nuclei of the Purkinje elements are often quite irregular in shape, and may have a crenated aspect due to pressure of the sarcoplasmic granules against the nuclear membrane. In the larger fibers the myofibrils occur in small bundles or run independently from each other in the abundant sarcoplasm, but in most cases they occupy the periphery of the fiber. These structural details, plainly visible in silver preparations, are still better seen in sections stained with the Masson trichrome technique (Fig. 10).

b. Innervation.—As is the case with the superior part of the main bundle, the right and left bundle branches of the dog are not supplied by parasympathetic nerve fibers. That absence of the latter is not the result of faulty impregnation is shown by the fact that the parasympathetic plexus in small arterial branches which occur here and there in the vicinity of the Purkinje strands is well impregnated. The occurrence of sympathetic innervation cannot be either denied or affirmed with the technique used, but the paucity of pale fibers in the

⁶This opinion is based on study of the hearts of calf embryos in the splendid embryologic collection of the Department of Zoology of Cornell University. The author is indebted to Dr. B. F. Kingsbury and Dr. H. B. Adelman for courtesies extended to him during his visit to their laboratory.

vicinity of the branches indicates that the participation of the sympathetic in the innervation of the Purkinje strands must be limited.

As already stated, in the monkey, parasympathetic fibers extend into the proximal (or initial) portions of the bundle branches. The fibers course in nerve bundles which become progressively smaller and finally disappear. The more distal portions of the conductive system in the ventricles lack a parasympathetic nerve supply.

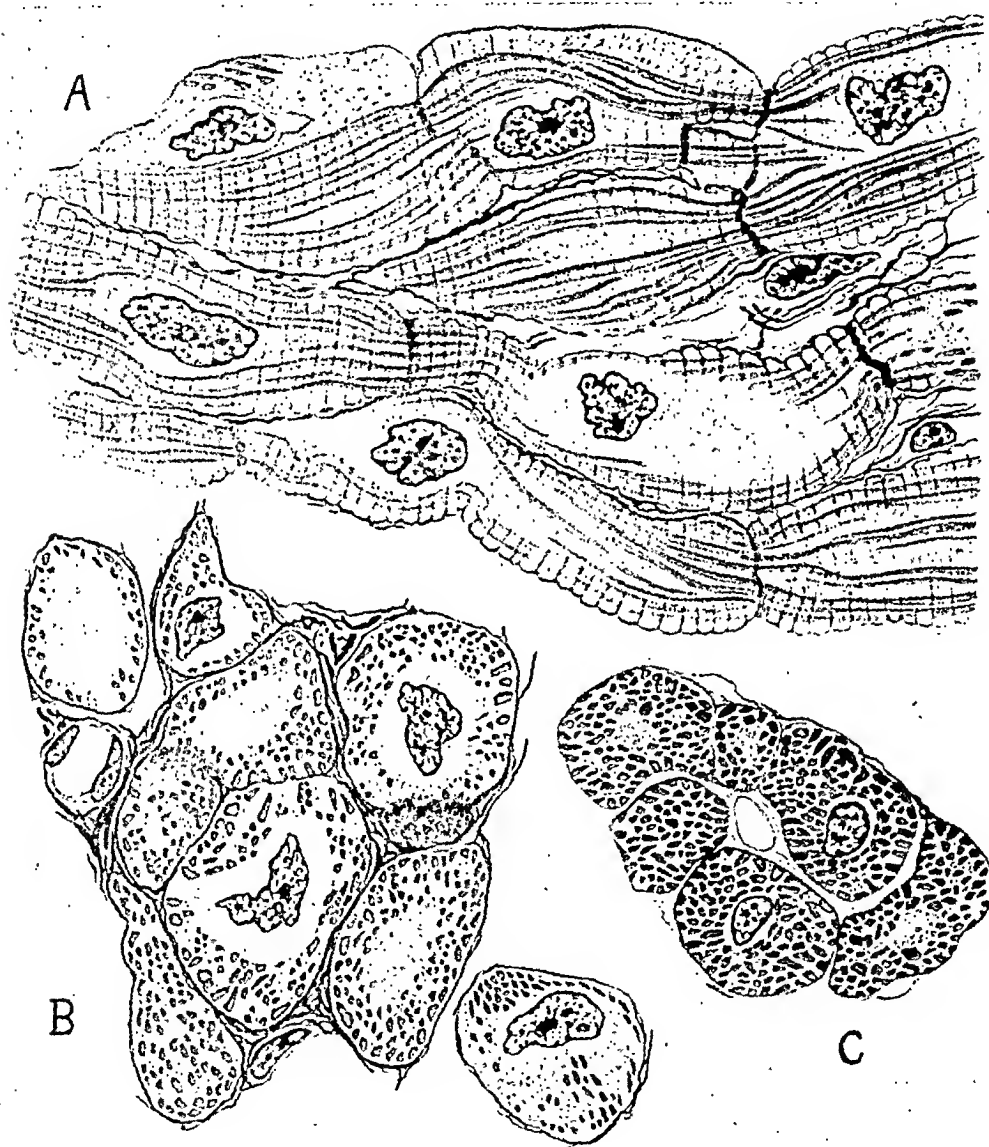


Fig. 10.—Rhesus monkey. *A* and *B*, Purkinje fibers of the left bundle branch in longitudinal and transverse section, respectively; *C* transverse section of ordinary myocardial fibers. Bouin's fluid; Masson trichromic technique.

Nerve terminations among the Purkinje fibers have been described in the calf and sheep by all authors who have studied the innervation of the heart in these animals. According to Vitali,¹⁷ the nerve fibers are very numerous, and, through multiple branchings, they give rise to a complex plexus enveloping the Purkinje strands; he regards these

fibers as afferent. A study of the figures by this author leads me to believe that the fibers described by him are not nervous, but that they belong to the argyrophil reticulum which is present everywhere in the heart.

5. *The Parasympathetic Innervation of the Atrial Myocardium.*—An interesting feature of the nerve supply to the heart is the participation of the parasympathetic nerve fibers (axons of the neurons of the intrinsic ganglia) in the innervation of the atrial and auricular myocardium. This is in contrast with the nerve supply to the myocardium of the ventricles, which is by means of sympathetic postganglionics from the middle cervical, stellate, and upper thoracic ganglia. Fibers arising from these ganglia also reach the atria, but, with the technique used, it is impossible to learn their ultimate destination.

The existence of ganglion cells to supply the cardiac muscle fibers is known through the researches of Dogiel,¹⁸ Woollard,¹⁹ Lawrentjew,²⁰ and Nonidez.² Woollard expressed the view that the greater part of the parasympathetic nerve fibers supply the supraventricular portions of the heart. This has been confirmed with the chloral hydrate-silver technique because of the strong affinity of the axons of the ganglion cells for the silver. In the monkey, in which the initial (proximal) portions of the right and left bundle branches are supplied by parasympathetic postganglionics, the contrast between these portions and the ventricular myocardium is quite marked. I have been able to follow the right bundle branch in serial sections of the interventricular septum, and, although deeply stained nerve fibers are seen ending within the branch, in no case have I seen terminations in the surrounding myocardial fibers.

The mode of termination of the parasympathetic nerve fibers on the atrial myocardium is similar to that described for the nodes; contact with the muscle fibers is effected by means of terminal and subterminal rings, minute club-shaped dilatations, and reticulated swellings (Nonidez,² Figs. 8 to 12). The terminations of the sympathetic postganglionics in the ventricles (as seen with other impregnation techniques) are very similar to those of the parasympathetic fibers.

The branches of the parasympathetic postganglionics ending on the atrial myocardium do not seem as numerous in the adult as in the hearts of very young animals. Whether branching of the nerve fibers increases in complexity after birth is difficult to say, but my impression is that a good deal of spacing takes place.

III. DISCUSSION

These observations on the structure and distribution of the conductive system are in substantial agreement with views currently held. Indeed, in young hearts it is possible to follow the distribution of the conductive system better than in the adult because serial sections can be obtained without an undue amount of labor, and the distances in-

volved are shorter. The same can be said of the hearts of small animals. In impregnations of frozen sections of the entire heart of the rat with the Bielschowsky-Gros technique, Lawrentjew and Gurwitsch-Lasowskaja²¹ found that the A-V node and main bundle take the silver more rapidly than the surrounding structures, and thus can be readily detected under low magnifications.

Although there are reports on the innervation of the conductive system,^{10, 13, 17, 19, 21} the techniques used by these authors did not permit differentiation of the parasympathetic from the sympathetic innervation. With the procedure employed by the present writer it is possible to identify and, in favorable cases, trace the parasympathetic postganglionies to their terminations. As already stated, some of these fibers (axons of the neurons of the intrinsic cardiac ganglia) end in the nodes and atrial myocardium, whereas others course with the branches of the coronary arteries in the ventricles, as well as in the atria. At present it is impossible to say whether there are direct efferent vagus fibers, for reasons already stated. The physiologic evidence, however, shows that destruction or paralysis of the ganglia of the S-A junction of the dog leads to a loss of chronotropic influence.⁶ Similarly, in the cat, nicotine injection not only prevents the chronotropic effect, but it also suppresses the inotropic.⁹

The relatively small numbers of myofibrils, greater abundance of sarcoplasm, and presence of glycogen in the Purkinje fibers have been regarded as important structural factors in the rate of their conduction and refractory period. In other parts of the system, specially in the nodes, the fibers are finer and their glycogen content smaller; indeed, the finest fibers and lowest glycogen content are said to occur in the A-V node, and this has been invoked to explain the slower conduction through this structure.²² However, recent observations by Goss²³ on rat embryos show that the pause between the atrium and ventricle already occurs in the early heart before differentiation of the conductive tissue has taken place, and that it approximates the adult value. In the light of these observations, it seems probable that the role of the rich parasympathetic innervation of the A-V node is a subsidiary one, i.e., it increases the A-V interval upon vagal stimulation. Since the nerve terminals are more numerous than in the S-A node, the greater influence of the vagus on the A-V node²⁴ and the production of block upon electrical excitation of this nerve can be accounted for. Similarly, we would find an explanation of the A-V block induced by digitalis in cases of auricular fibrillation, and of the effect of morphine in producing a similar effect through central excitation of the vagus.²⁵ The injection of pitressin or neosynephrin frequently interferes with conduction; the reflex slowing occurs via either vagus, but only the nerve on the left side exerts sufficient effect on A-V conduction to produce block,²⁶ a result which is in accord with

the histologic observations, for most of the nerve supply to the A-V node and bundle is from ganglia receiving preganglionics from the left vagus. Of further interest is the coincidence of the area of richest innervation of the A-V node of the dog with the "susceptible region" of Lewis, White, and Meakins.²⁷

Another interesting feature is the absence of parasympathetic innervation of the lower (or distal) portions of the conductive system, which are lodged within the septum and ventricular walls. In the dog this is also true of the main bundle and the bundle branches, whereas, in the monkey, the proximal part of the latter contain nerve endings. It has been claimed that, after destruction of the canine A-V node and bundle, the vagus still exerts an influence on the idioventricular rhythm. However, Jourdan and Froment,¹⁴ who have reported this effect, admit that in about 50 per cent of the dogs the influence was so weak that it could be detected only after the injection of eserine. They accordingly suggest that vagus impulses reach the ventricles through devious paths. That the vagus normally exerts little or no action on the ventricles is now generally accepted. Furthermore, the experiments of Wiggers,²⁸ carried out in the course of many years, show that vagal excitation fails to abolish ventricular fibrillation produced in various ways.

As noted before, the axons of the neurons of the intrinsic cardiac ganglia (parasympathetic postganglionics) are widely distributed throughout the heart, but the only muscular structures supplied by them are to be found in the supraventricular regions. In addition to the postganglionics ending in the conductive system, there are fibers which establish contact with the ordinary myocardial fibers of the atria and auricles (appendages). The separate chronotropic and inotropic effects which follow excitation of the vagus thus rest on an anatomic basis. Heinbecker and Bishop⁹ have shown that, during recovery from nicotine poisoning, stimulation of the vagus of the cat causes a slowing of the heart before the inotropic susceptibility has been recovered. This they have interpreted as indicating that there are nerve fibers which cause the chronotropic depression, whereas others produce the inotropic effect only. In either case, transmission of the nervous impulse is through ganglion cells.

The parasympathetic innervation of the S-A and A-V nodes, respectively, accounts for the marked influence of the vagi on conduction. Whether there is sympathetic innervation of the nodes could not be ascertained with the technique used in these studies. The same can be said in regard to the possible occurrence of sympathetic terminations in the atrial myocardium; should they be present, then the atrial muscle fibers would have a double innervation, as opposed to those of the myocardium of the ventricles, which are supplied solely by the sympathetic. The existence of a parasympathetic innervation of the supra-

ventricular myocardium may be related in some way to the absence of specialized muscle fibers connecting the nodes.

SUMMARY

1. A study of the impulse conducting system in the hearts of puppies and one rhesus monkey, prepared with the chloral hydrate formula of the Cajal silver nitrate technique, has confirmed the observations of previous investigators. In addition to the S-A and A-V nodes (Fig. 1), there is a distinct main bundle (Figs. 5, 6, and 7) which divides into right and left bundle branches. The latter and their ramifications are composed of swollen fibers, with small numbers of myofibrils, abundant sarcoplasm, and irregular nuclei. These fibers connect at various levels with the musculature of the ventricles (Fig. 9, right); in the puppy they resemble closely the typical Purkinje fibers of the calf, sheep, etc. (Fig. 9, left), whereas, in the monkey, they are less differentiated but nevertheless quite conspicuous (Fig. 10, A and B).
2. The S-A and A-V nodes, respectively, are supplied by axons of neurons of the intrinsic cardiac ganglia (parasympathetic postganglionies), but the nerve terminals are much more numerous in the A-V node (cf. Fig. 2 with Fig. 4). Whether there is a sympathetic nerve supply to the nodes could not be ascertained because the technique used does not impregnate sufficiently the sympathetic postganglionies.
3. The main bundle and bundle branches of the dog lack parasympathetic nerve endings. In the monkey these nerve terminals occur not only in the main bundle (Fig. 8), but also in the proximal portions of the right and left bundle branches. Parasympathetic nerve endings are absent in the ramifications of the bundle branches in the two species.
4. The rich parasympathetic nerve supply to the A-V node, as compared with the innervation of the S-A node, may account for such phenomena as the production of A-V block through electrical stimulation of the vagus, the similar effect produced by morphine, by digitalis in cases of auricular fibrillation, etc., and, in general, the greater influence of vagal stimulation on the A-V node.
5. The existence of a parasympathetic innervation of the ventricles, suggested by the effect of excitation of the vagus after the A-V bundle has been crushed, is questioned. The variable effects on the idioventricular rhythm reported by Jourdan and Froment cannot be explained on an anatomic basis.
6. The anatomic basis for the inotropic effect of the vagus is indicated by the existence of parasympathetic nerve endings in the atrial and auricular musculatures.

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CAPILLARY STUDIES IN MIGRAINE; EFFECT OF ERGOTAMINE TARTRATE AND WATER DIURESIS

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INTEREST in the phenomena underlying attacks of migraine has led to attempts to explain the mechanism involved. Graham and Wolff¹ were able to show that dilatation and increased amplitude of pulsation of the branches of the external carotid artery occurred during the attack, and, because reduction of the pulsation relieved headache, concluded that this fact was important to the mechanism of production of an attack. Kennedy² and others believe that local edema in the brain substance might be the cause of the attack. These two concepts are, a priori, not contradictory, in that, with increased pulsation, arteriolar dilatation may be inferred, and, under these circumstances, fluid might more readily pass through the walls of capillaries. Since exchange of fluid substances between the blood and the tissues occurs chiefly through the endothelial wall of the capillaries,³⁻⁵ it was believed that study of capillary behavior in migraine might be fruitful.

The capillaries of the surface of the skin, as viewed by direct microscopy in man, vary in different areas. Morphologically, two main types are recognized. Over most of the surface of the body, the peripheral vessels are arranged in a network (*rete mirabile*).^{6, 7} The second type forms a so-called terminal circulation, the vessels of which are referred to as "end capillaries." In such regions as the base of the cuticle of the fingers and toes, the skin over the tibia,⁸ and the gingival papilla⁹ there is a fairly regular and horizontal arrangement of the loops. This permits observation of the blood flow through portions of the capillary which may be distinguished as an arterial limb, a venous limb, and an intermediate part connecting the two, often referred to as the transitional limb.

In order to describe as objectively as possible the appearance of surface capillaries, the following observations have in each instance been commented upon:

1. Form of the individual capillary loops and arrangement in the field.
2. Diameters of the arterial, venous, and transitional limbs.
3. Occurrence of the blood flow and, when present, its speed and regularity.

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The studies were initiated by Dr. M. E. O'Sullivan, in charge of the Migraine Clinics at Bellevue Hospital and New York University College of Medicine.

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4. Visibility of the vessels in the deeper layers of the arterial and venous limbs and the subpapillary plexus.

5. Distinctness of the capillary outline.

Although most of these characteristics have been referred to extensively in the literature, variation in the distinctness has generally been regarded as caused by the specific nature or character of the skin, or to technique, when indirect illumination was used. Deutsch¹⁰ has, however, very recently reported a direct relationship between decreased visibility and increased permeability of the capillaries.

METHOD

The first report of direct observation of the capillaries of the human skin was published by Lombard,¹¹ in 1912. Cedar oil was placed on the surface of the skin at the base of the cuticle to obtain a homogenous refracting medium, a cover glass was placed upon the oil, and the field was illuminated from the side. The basic principles of this method have been used up to the present time, and have been modified only in that the use of the cover glass has been dispensed with, the illumination improved, and special microscopes devised.

Certain limitations exist in using microscopic examination of capillaries as a guide to the nature of vascular responses: (1) It is subjective. This defect can be remedied to a certain extent by employing a camera, either still or moving, but, even here, interpretation is difficult. This is true especially with regard to distinctness of outline because of the possibility of shift in position during the taking of a picture. (2) It takes account of so few of the many capillaries involved in a vascular pattern. (3) It can be employed only on or very near the surface (skin or mucous membranes). For our purpose it was found advantageous to employ the base of the cuticle for studies of the skin, and the inner surface of the lower lip for studies of the mucous membranes. These sites were chosen because the regions are readily accessible to the objective lens of the microscope, the arterial and venous limbs of the capillaries can be observed over a greater distance, and because they are "end capillaries."

The source of light was either an automatically adjustable, air-cooled electric light, equipped with heat absorbing glass filters, or a carbon arc lamp and a water-cooling cell filled with 1 per cent nickel chloride solution. For the study of mucous membranes the "Ultrapak" device was most serviceable. Observations were made with magnifications of 60 or 70 diameters. For direct photography of the field, a beam splitting mechanism was used.

The data in this report were obtained from the examination of 118 patients (of whom 108 were photographed) in the Migraine Clinics at Bellevue Hospital and New York University College of Medicine.

OBSERVATIONS

Preliminary observations on patients during migraine attacks indicated the occurrence of a regular tendency to indistinctness or "blurring" of the capillary outline; this was less marked during the interval between attacks. Particular attention was thenceforth given to the observation of this phenomenon; since the conditions of observation

were relatively constant, it seemed likely that changes in distinctness might indicate a change in physiologic state. Indistinctness of the capillary outline was also observed in women during menstruation, and occasionally in other persons.



Fig. 1A.—“Normal” capillary loops photographed in the skin at the base of the cuticle of a healthy young adult male. Note that the hairpinlike forms have arterial limbs narrower than the transition and venous limbs. There are a few slight convolutions and single crossings.

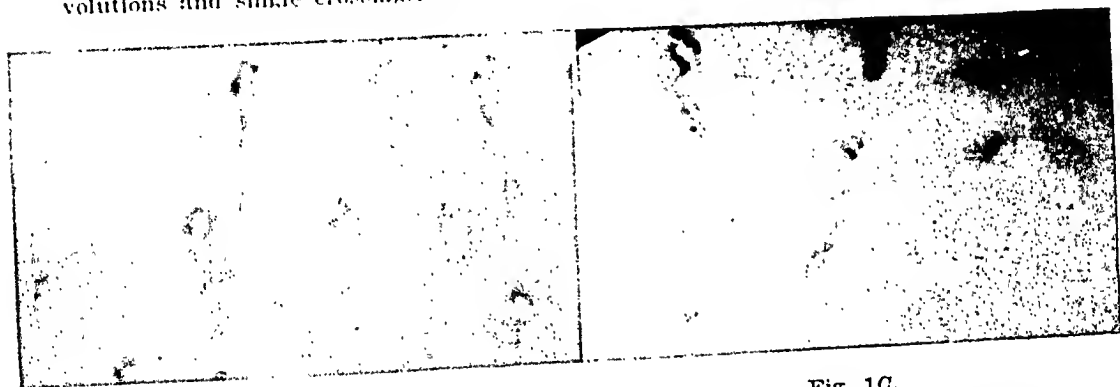


Fig. 1B.

Fig. 1C.

Fig. 1B.—Capillary loops in the skin at the base of the cuticle of a 42-year-old female migraine patient, who also showed marked clinical signs of an endocrine disturbance (i.e., obesity, hirsutism, oligomenorrhea). Note that the capillaries show many of the changes specified as modifying the basic characteristics of the loop. Compare with Fig. 1C.

Fig. 1C.—Capillaries photographed in the interproximal papilla of the gingiva adjacent to the oral mucosa, of the same patient as shown in Fig. 1B. Note the presence of very similar changes.

Of the total of 118 migraine patients who were studied, repeated observations, on which this report is based, were made on 98. We observed differences in the form of the capillaries of these patients which may be appreciated best by comparison with the hairpinlike form of normal end capillaries (Fig. 1A). The appearance of the loop differed from the normal in its basic characteristics (Fig. 1B) in 88, or roughly 90 per cent, of the patients. These differences consisted of an increase in tortuosity of the limbs of the capillary loop, increase in the number of crossings, and the occurrence of knobblings in the different limbs. Variations in diameter of the different limbs, of long or short duration, occurred in 78, or about 80 per cent, of the patients. Differences in appearance and variations in width were found to be present simultaneously in 63, or about 65 per cent, of the patients. Similar deviations from the normal were found in the capil-

laries of the mucous membranes of the inner surface of the lower lip in 22 cases (Fig. 1C).

The blurring was found to be present during migraine attacks and absent or diminished during the headache-free interval in over three-fourths of the cases. The state of visibility varied even during the period of a single observation. The distinctness of the capillary was influenced by intravenous injection of ergotamine tartrate during an attack, the pattern of which is described later in this paper. Simultaneous observations were made on the capillaries of the skin at the base of the euticle and on the mucous membranes of the mouth, and showed parallel changes. In any one observation, the mechanical setup remained unaltered throughout, and comparisons were made with the sharpest focus obtainable in the given field.

EFFECT OF ERGOTAMINE TARTRATE UPON THE SURFACE CAPILLARIES IN MIGRAINE ATTACKS

Numerous observations¹²⁻¹⁶ tend to show that ergotamine tartrate is effective in terminating the migraine attack. According to Lemox and Leonhardt,¹⁷ the beneficial effect is due, at least in part, to an increase in arterial tone, arterial pressure, and rate of blood flow, together with a decrease in blood volume. Graham and Wolff¹ consider migraine to be directly related to the amplitude of pulsation of branches of the external carotid arteries, and relief from the attack by ergotamine was correlated with constriction of these arteries and reduction in amplitude of their pulsation.

METHOD

The peripheral capillary effect of an intravenous injection of 0.25 and 0.5 mg. of ergotamine tartrate* during the migraine attack was watched under the microscope, and photographs were made in twenty-three instances in sixteen patients. During the period of observation the patient was in the recumbent position, with the hand extended at approximately the heart level.

OBSERVATIONS

Characteristic capillary changes were observed to follow injection of the drug in a specific sequence.

Two to five minutes after the injection, the original "blurring" tended toward alternation between clearing and indistinctness. During this interval pronounced variations in diameter also took place. The indistinctness tended to increase with nausea. Eight to fifteen minutes after the injection, the capillaries appeared much clearer and narrower, and subjective relief was simultaneously experienced by the patient. Subsequently, the distinctness of the capillary outline again varied markedly. Thirty to forty-five minutes after the injection, the loops again became blurred.

*The ergotamine tartrate was "Gynergen" (Sandoz).

It has been indicated in the previous section that the capillaries of the skin at the base of the cuticle and on the inner surface of the lower lip behaved similarly as to changes in form and degree of visibility. Simultaneous observations and photographs in these sites made in two instances after ergotamine tartrate injections during migraine attacks (Figs. 2A, B, C, D) showed that the onset, duration, and sequence of the modifications, as noted above, coincided throughout in the two regions.



Fig. 2A.

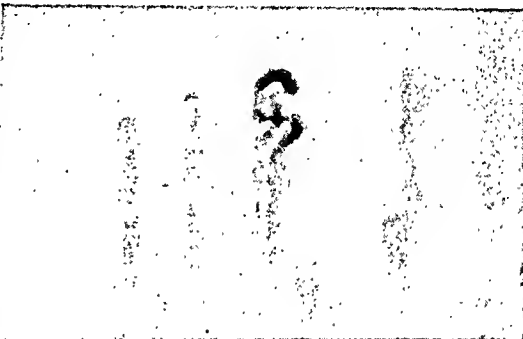


Fig. 2B.

Fig. 2A.—Capillary loops in the skin at the base of the cuticle of an adult male during a severe migraine attack. The visibility of the capillaries is less clear than in Fig. 2B.

Fig. 2B.—Identical field in the skin at the base of the cuticle of the same patient as shown in Fig. 2A. Photograph was taken ten minutes after the intravenous administration of 1.0 c.c. ergotamine tartrate (1:2,000), while the loops showed clearer visibility and the migraine attack had been alleviated subjectively.

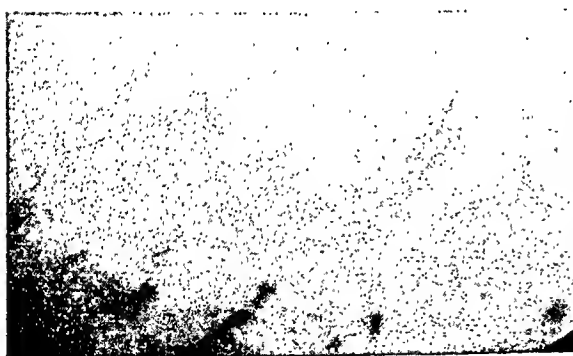


Fig. 2C.

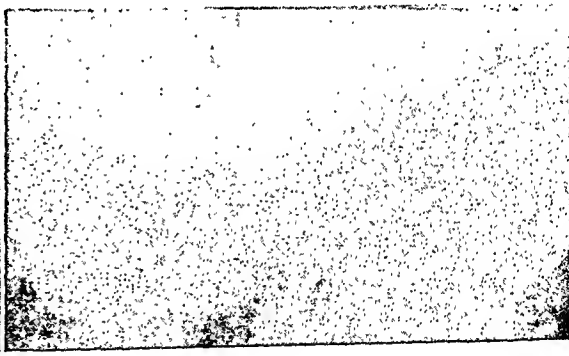


Fig. 2D.

Fig. 2C.—Capillary loops in the mucous membrane of the inner surface of the lower lip, near the vermillion border, taken of the same patient as shown in Fig. 2A during the same migraine attack. Note the poor visibility of the capillary outlines and the similarity to the state shown in Fig. 2A. Compare also with Fig. 2D.

Fig. 2D.—Similar field, of the same region as shown in Fig. 2C. The photograph was taken fifteen minutes after the intravenous administration of 1.0 c.c. of ergotamine tartrate (1:2,000), when the vessels showed decreased "blurring" and the migraine attack was relieved.

STUDIES ON WATER DIURESIS

The visibility changes reported in the preceding sections indicated the possibility that a disturbance in the water balance existed during the migraine attack. Effort was made, therefore, to study, in migraine patients, the effect of the ingestion of 1,500 c.c. of water. Venous

pressure readings and capillary microscopy were carried out on fifteen migraine patients in twenty-nine experiments. Venous pressure was measured in all but three cases; capillary observation and photography were carried out in sixteen experiments.

Vollhard and Fahr¹⁸ have shown that the ingestion of 1,000 to 1,500 c.c. of water by a normal adult induces the output of a quantity of urine slightly in excess of the amount ingested, within four hours. A quantity of urine in excess of half of the amount ingested is excreted within the first two hours. The specific gravity usually falls as low as 1.002 in the second hour. A dry meal, given four hours after the ingestion of the fluid, is usually followed by the voiding of a small volume of urine within the next four to six hours, the specific gravity of which may reach a concentration of 1.028 to 1.032.

PROCEDURE

Since the results of the Vollhard and Fahr test have been shown to be modified by renal and circulatory insufficiency, it was ascertained that these conditions did not exist in the patients tested. All the tests were begun early in the morning, after the subject had fasted for about twelve hours. The patient voided before ingesting the water. The subject remained at rest in bed throughout the test. A total of 1,500 c.c. of tap water was ingested by mouth within five to ten minutes. The volume of urine excreted and the specific gravity were measured every hour for four hours, and every other hour for another four hours after the administration of a dry meal.

Venous pressure was measured by means of the indirect method of Eyster and Hooker,¹⁹ rather than the method of Moritz and v. Tabora,²⁰ because it permits frequently repeated readings, is rapid and painless, does not cause any marked interference with the circulation, and the readings compare fairly closely with those obtained by the direct method except for the effect of tissue pressure.²¹ The indirect method can, however, be employed only on persons with clearly visible venous channels on the forearm or dorsum of the hand.

RESULTS

The results of twenty-nine experiments on fifteen patients are as follows:

1. Fourteen of the fifteen migraine patients showed an abnormal "excess excretion" rate within the period of the dilution experiment.* As this excess excretion subsided, a migraine attack developed in twenty-one of the twenty-nine experiments. Excess excretion was maintained throughout the concentration period† in four instances, and in none of these did a migraine attack develop. In four instances, relief of the migraine attack occurred, together with a second increase in urine flow.

*The four hours after taking 1,500 c.c. of water.

†The four hours after eating the dry meal.

2. In two cases, 0.5 mg. of ergotamine tartrate was injected intravenously at the height of the migraine attack which had developed with complete cessation of urine flow. In both instances relief set in with diuresis and profuse perspiration.

3. Small and inconstant venous pressure variations occurred in four instances; no headache developed. In fifteen instances the venous pressure dropped simultaneously with the cessation of urine flow and the development of an attack, and remained low throughout the attack (Table I).

TABLE I

SUMMARY OF VENOUS PRESSURES IN RELATION TO DEVELOPMENT OF HEADACHE AFTER FORCED FLUID INTAKE IN MIGRAINE PATIENTS

No. of experiments	HEADACHE DEVELOPED			HEADACHE DID NOT DEVELOP			ERGOTAMINE TARTRATE INJECTED AT HEIGHT OF HEADACHE		
	15			9			2		
	BEFORE FLUID INTAKE	LOWEST AFTER FLUID INTAKE	HIGH-EST AFTER FLUID INTAKE	BEFORE FLUID INTAKE	LOWEST AFTER FLUID INTAKE	HIGH-EST AFTER FLUID INTAKE	BEFORE FLUID INTAKE	LOWEST AFTER FLUID INTAKE	HIGH-EST AFTER FLUID INTAKE
Range of venous pressure in cm. water	7-10	4-8	10-17	5-11	4-9	6-15	9-9	6-8	13-14
Average of venous pressure in cm. water	8.6	5.9	12.8	7.9	6.9	11.2	9.0	7.0	13.5

4. The majority of patients did not show blurring of the capillaries or suffer from headache before ingestion of the fluid. Although about half exhibited slight blurring of the capillaries and complained of slight headache during the period of dilution, the noticeable fact is that, during the period of concentration, half of the patients showed marked blurring of the capillaries and complained of severe headache (Table II).

TABLE II

STATE OF CAPILLARY VISIBILITY AND HEADACHE DURING THE PHASES OF THE VOLIARD AND FAHR TEST

CAPILLARY VISIBILITY AND HEADACHE	BEFORE INGESTION	DURING DILUTION	DURING CONCENTRATION	TOTAL
No blurring and no headache	8	6	0	14
Slight blurring and no headache	4	2	2	8
Slight blurring and slight headache	2	7	3	12
Slight blurring and marked headache	0	0	1	1
Marked blurring and slight headache	0	0	2	2
Marked blurring and marked headache	1	0	7	8
Total	15	15	15	

5. In one instance ergotamine tartrate was administered intravenously four hours after ingestion of water, at the height of the headache. Some blurring of the capillaries had been present from the beginning of the observation, but, after the injection, the blurring became slightly less, and varied greatly along with the occurrence of diuresis and cessation of headache (Fig. 3).

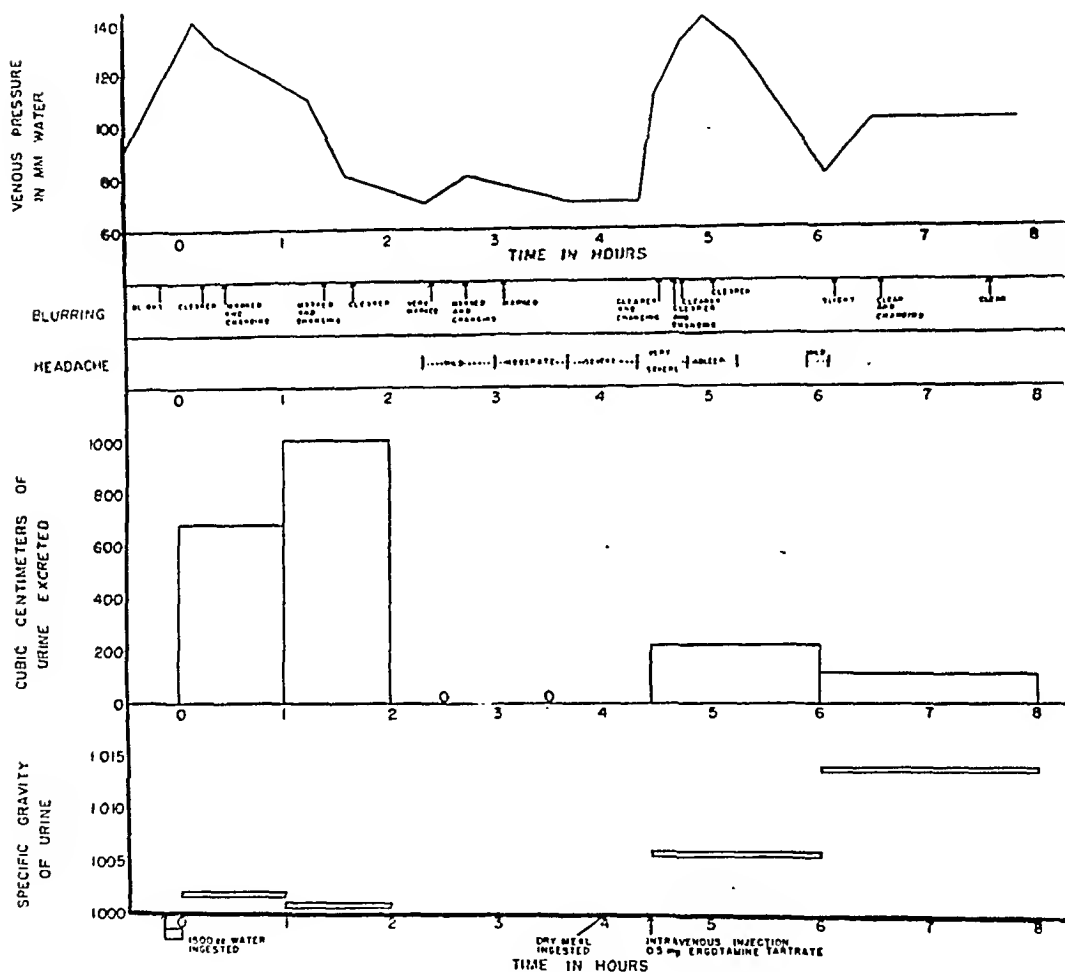


Fig. 3.

6. Only one of the fifteen patients, a woman, 18 years of age, showed an almost normal excretion curve. She was also the only one of the group whose age was under 30 years. According to her history, the migraine attacks from which she had suffered had been of infrequent occurrence and of a mild nature.

DISCUSSION

Any critical evaluation of the results of capillary microscopy and photography depends upon adoption of definite criteria for deciding

upon the limits within which a capillary blood vessel may be called normal, and upon appreciation of the sources of error and limitations of the methods. The normal capillary structure has been described by many investigators. Slight changes in diameter, a wavy course of the capillary, and irregularities in blood flow, as described by Parrisius²² and more recently by Griffith,²³ are so common as to suggest that they belong within the range of normality.

Disturbances in the endocrine status of the subject have been reported²⁴⁻²⁶ as giving rise to variations in the length and diameter of the visible capillary limbs, the distance between the arterial and venous channels, the pointing of the transition limb into "tent formation,"²⁷ the rate of blood flow, and the reactions to drugs such as epinephrine.^{28, 29} Previous attempts to label definite "capillary pictures" as characteristic of certain diseases have failed largely because the microscopic changes are not usually specific for a given disease. The method is useful essentially as an additional means of study of physiologic and pathophysiologic changes in the peripheral circulation.

The significance of "blurred" capillaries in migraine needs evaluation. Explaining the observed blurring as the result of technical difficulties does not seem valid because blurring occurred so regularly in a given patient during an attack of migraine, and because the same field and mechanical setup were used. Furthermore, the change was simultaneous in skin and mucous membranes. In photographs of capillaries, blurring was difficult to interpret because the accuracy of focus could not be ascertained with sufficient reliability. The focus may change in the unanesthetized living subject during exposure of the film because of the limited fixation of the part studied. Observation is obviously superior to photography for studying changes in visibility.

Change in the state of visibility of the capillary outline was reported by Cohnheim³⁰ to occur in inflammation, and was believed to be related directly to swelling of the endothelial cells of the capillary walls. During wheal formation, increasing capillary indistinctness has been observed to culminate in a final capillary tamponade.³¹ The experiments in diuresis also suggest that the distinctness of capillary outlines is directly related to the transudation or exchange of material through the capillary wall. Occurrence of blurring in the capillaries of the body surface does not, however, permit the assumption of similar changes in the cerebral capillaries, even though similarity in the response of the capillaries of the two regions in question has been described.³²⁻³⁴

In contrast to the changes in the state of visibility, changes in the form of the capillaries can be recorded with more accuracy. The significance of deviations in form which alter the basic characteristics of the loop is not sufficiently understood. It is difficult to state what deviations from the normal are to be considered as reactive, regressive, or the result of failure in development of capillaries. The variability

in diameter recalls the "angioneurotic diathesis" described by Parisius²² and Mueller.³⁵ It has been recently indicated by Mueller³⁶ that persons who have such changes in capillary form and diameter tend to have an increased susceptibility to vasomotor disturbances, allergy, and migraine.

The mechanism of the action of ergotamine tartrate is not fully understood. Our observations suggest the existence of a relationship between the fluid exchange through the capillary walls, and relief of some of the symptoms of the migraine attack by the action of ergotamine tartrate. Additional information regarding the effect of ergotamine tartrate on the capillaries in normal persons and in the interval between migraine attacks is needed.

The studies on water diuresis indicate a relationship between the water balance of the body, the state of the peripheral capillaries, and the migraine attack. Forced ingestion of water induced an excessively high rate of excretion in fourteen of fifteen migraine patients, a fact which suggests that the pre-edematous state of Volhard and Fahr¹⁸ existed. Fremont-Smith and Merritt³⁷ have reported that the induction of epileptiform seizures by forced fluid intake takes place in the absence of changes in intraeranianial pressure. It is therefore unlikely that the development of headache after forced fluid intake in our studies was mediated by changes in intraeranianial pressure.

A correlation in time between urine flow and onset and alleviation of the headache was consistent in the reported experiments; cessation of urine flow coincided with the onset of headache in the twenty-one instances in which an attack developed. Further, in the two instances in which ergotamine tartrate was administered intravenously at the height of the attack, the relief of headache coincided with a dramatic resumption of diuresis.

The variations in venous pressure were not large enough to be clear in significance. The fact that venous pressure fell slightly in each instance of an induced attack of migraine may be considered as additional evidence of loss of fluid from the circulatory system into the tissues.

SUMMARY

1. An attempt was made to study changes in the capillaries of the body surface with respect to their possible relationship to the migraine attack.

2. Impaired visibility of the surface capillary outlines, or "blurring," was observed during 142 migraine attacks in 118 patients. Its possible relationship to a physiologic mechanism is discussed.

3. Changes in the visibility of the surface capillary vessels were found to follow a definite course subsequent to intravenous injections of 0.25 or 0.5 mg. ergotamine tartrate, in twenty of twenty-three instances.

4. Observations during migraine attacks induced by forced water ingestion seem to indicate a definite relationship between the fluid balance of the body, the state of the peripheral capillaries, and the migraine attack.

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THE BLOOD PRESSURE IN ESSENTIAL HYPERTENSION: EFFECT OF SEVERAL REPUTEDLY HYPOTENSIVE DRUGS

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ESSENTIAL hypertension is an extremely widespread disease. It has been estimated by one author¹ that almost a fourth of all deaths of persons more than 50 years old are directly attributable to hypertension. The leading position of cardiovascular-renal diseases in tabulations of causes of death is familiar to all. Hypertension accounts for a large percentage of these deaths. In a series of 150 cases of cardiac decompensation, Dry² found that in 76 per cent of cases "cardiac decompensation was on the basis of hypertension and coronary disease either independently or in association with each other. . . ." The influence of elevation of the blood pressure on life expectancy has been clearly demonstrated by Keith, Wagener, and Barker.³ These authors found that even in the "benign" or relatively stationary types of essential hypertension, the median duration of life after the first examination is 100 months (8.3 years) for patients who have a minimal, or group I, classification. Among their patients with maximal, or group IV, hypertension, the median duration of life after the first examination was but 5.4 months. This has been confirmed by others.⁴ Thus, there is an ample stimulus for search for improved treatment for this widespread disease.

In the more than forty years that have elapsed since Allbutt⁵ described the syndrome of essential hypertension—indeed, in the century or more since Bright initiated interest in problems regarding high blood pressure, a successful, practical, and safe method for the routine treatment of essential hypertension has not been devised. Many drugs have been advocated for the medicinal treatment of high blood pressure. Casual perusal of a recent listing⁶ of drugs and pharmaceuticals reveals almost 100 names of "hypotensive" drugs which are alleged to be of value in such treatment. In 1930, Ayman⁷ found at least 200 reports of the successful treatment of essential hypertension by different drugs and methods. He pointed out that the constant employment of new drugs and the continued high mortality rate associated with essential hypertension indicate that the proper treatment is still unknown. This statement might well have been made today. In this excellent review, Ayman pointed out certain fallacies in these claims, which are involved in the interpretation of therapeutic results. (Perusal of the literature of the

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subsequent decade would suggest that these pertinent warnings have been generally disregarded.) The claim of "successful" treatment of essential hypertension often is based only on symptomatic improvement of the patient, rather than on any substantial reduction of the blood pressure. Most authors agree that the symptomatic status of the hypertensive patient has little relationship to the levels of the blood pressure.⁸⁻¹¹ In a further discussion on the interpretation of "relief of hypertension," Ayman¹² pointed out additional pitfalls which claim the unwary. The most important of these is the lability of the blood pressure among hypertensive persons. Wide fluctuations in blood pressure from time to time necessitate¹³⁻¹⁶ making careful control observations to allow for appreciation of this factor in the treated patient. Otherwise, this striking instability may account for an apparent hypotensive effect. This factor also becomes an important consideration in the establishment of criteria for determination of a "hypotensive" effect.

The refractory nature of hypertension is further confirmed by the large number of medical techniques which continue to appear. It seems unlikely that all of the large number of drugs now available⁶ are capable of lowering the blood pressure in hypertensive patients. It is noteworthy that when the results of "successful" treatment are analyzed to show symptomatic improvement, as separate from actual reduction in blood pressure, it becomes apparent that, although symptomatic response is relatively easily obtained, reduction of blood pressure is difficult. Sometimes it is said that symptomatic improvement is a sufficient end in itself, and that reduction in blood pressure is undesirable; and that, if this latter condition is established, the patient may suffer. It is by no means demonstrated that such a statement is true, and experienced observers^{7, 17, 18} of hypertensive patients feel that, on the contrary, reduction of blood pressure is the essential aim of treatment. The fact that the symptoms of hypertension can be controlled in many ways,^{7, 19, 20} and that, with excellent symptomatic control easily available, the mortality rate has not been reduced over a period of years, would lead to the conclusion that the symptoms associated with hypertension do not measure any factor contributing to death in these patients. It seems more reasonable to conclude that elevated levels of blood pressure are significant contributory factors in the established mortality rate. Indirect support of this contention is seen in the advertising appeals of manufacturers, who often make extravagant claims for the hypotensive properties of their particular remedies.

In a more recent therapeutic assay of drugs which are reputed to be effective in controlling essential hypertension, Evans and Loughnan¹⁸ agreed that the desirable (that is, hypotensive) effect is rarely obtained, but that good symptomatic response can be obtained by the use of many drugs. In their series, placebo medication was generally as effective as any "hypotensive" drug that they used. These authors also pointed

can thus be made to describe all possible variations of the area under T_1 , T_2 , and T_3 due to all possible variations of the area under QRS. In a like manner, if the terminus of \hat{G} is made to describe any arbitrary path whatever about O while \hat{A}_{QRS} remains fixed, the terminus of \hat{A}_T describes an altogether similar path about the terminus of $-\hat{A}_{QRS}$. The second path can thus be made to describe all possible variations in the area under T_1 , T_2 , and T_3 due to all possible variations of the gradient. All possible secondary and primary changes, respectively, in the area under T may, in this manner, be arbitrarily obtained.

Assuming that the gradient is normal, the position of \hat{A}_{QRS} which gives the maximal negative area under T_1 is such that \hat{A}_{QRS} coincides with the positive half of the RL-axis. Under the circumstances, the net areas under QRS_2 and QRS_3 are equal in magnitude and unlike in sign; the former is positive and the latter negative. Again assuming that the gradient is normal, the position of \hat{A}_{QRS} which gives the maximal negative area under T_3 is such that \hat{A}_{QRS} coincides with the positive half of the LF-axis. Under the circumstances, the net areas under QRS_1 and QRS_2 are equal in magnitude and unlike in sign; the former is negative and the latter positive.

It has been herein pointed out that, within relatively narrow limits, the normal gradient \hat{G} is fixed with respect to \hat{H} . Inasmuch as the position of \hat{H} varies normally in one subject as compared with another, it is clear that the normal position of \hat{G} must likewise vary. It is also clear that the precise position of \hat{G} with respect to the triaxial reference system is of great importance in ascertaining whether the areas under T_1 or T_3 will be less positive or actually negative for the described critical positions of \hat{A}_{QRS} .

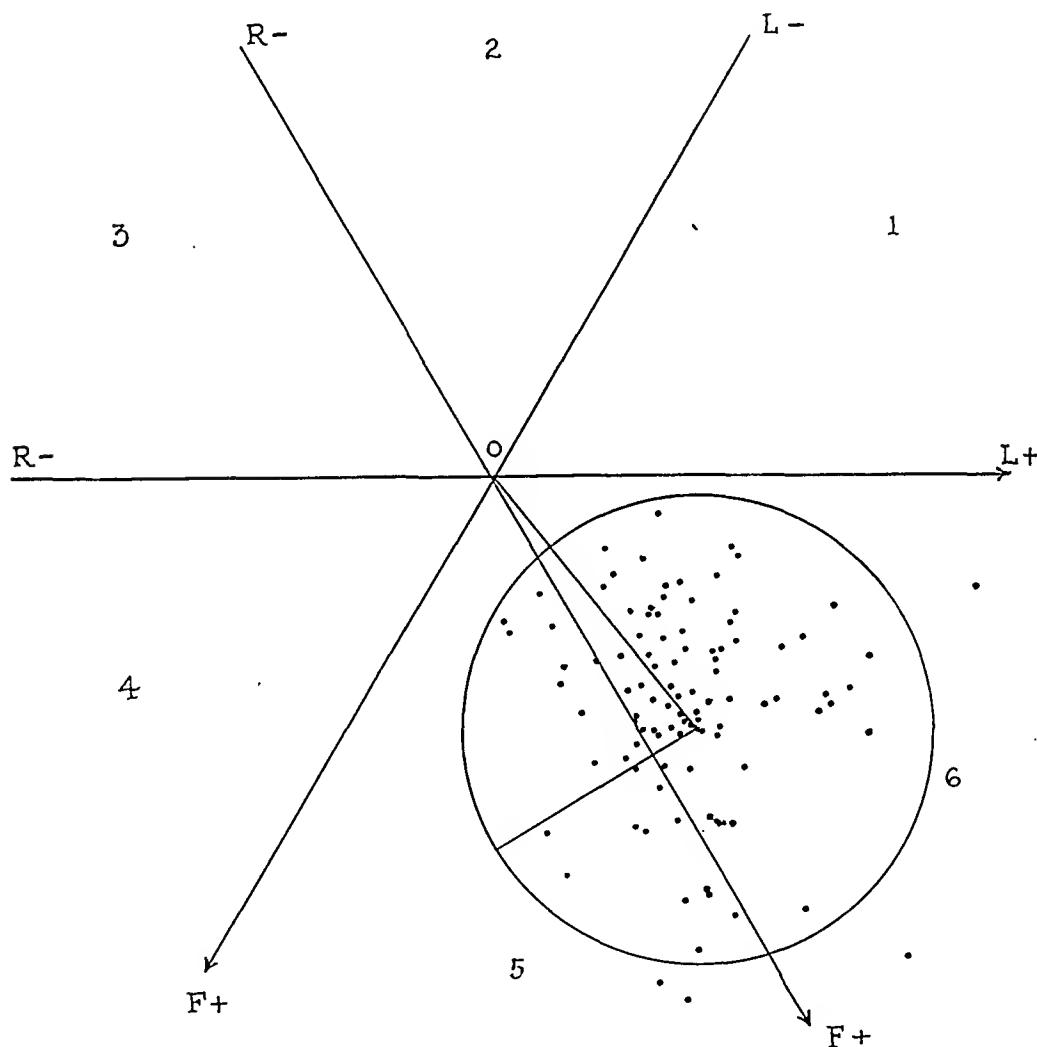
To illustrate, let us suppose that Subject A, with a vertical heart, has a normal gradient that lies in that half of the fifth sextant which is adjacent to the sixth. In addition, let us suppose that Subject B, with a horizontal heart, has a normal gradient at 3 o'clock, or collinear with the positive RL-axis. Let us further suppose that \hat{A}_{QRS} for both subjects is like in magnitude and lies at 3 o'clock. Furthermore, the appearance of QRS in both subjects is similar. In Subject A the situation is abnormal, for \hat{A}_{QRS} makes a polar angle of more than 60 degrees with respect to \hat{H} or \hat{G} (the maximal normal is about 30 degrees, Fig. 6). The abnormality of QRS is evidenced by the positive rotation (counterclockwise) with respect to \hat{H} or \hat{G} , and may be ascribed to preponderant hypertrophy of the left ventricle. Under the circumstances, T_1 is inverted and T_2 is low or diphasic. Moreover, the T-wave changes are secondary and add nothing further to the diagnosis. In Subject B the entire situation is within the range of normal. T_1 is necessarily a positive deflection unless the magnitude of \hat{A}_{QRS} actually exceeds that of \hat{G} . Since \hat{G} was assumed to be normal, the abnormality of \hat{A}_{QRS} must (in the event that T_1 is inverted) consist of an abnormal growth of A_{QRS} without rotation. A growth of A_{QRS} may result from ventricular hyper-

trophy. Therefore, in the event that A_{QRS} exceeds G , with consequential inversion of T_1 , the T-wave changes are secondary in kind, and add nothing further to the diagnosis of ventricular hypertrophy for Subject B.

Deviation of A_{QRS} with respect to the normal ventricular gradient:

Max. $+\angle = 24^\circ$, Mag. = 11.48 m.v.s.

Max. $-\angle = -35^\circ$, Mag. = 10.80 m.v.s.



A circle of radius 42 m.v.s. centered 58 m.v.s. from the origin at an \angle of -50° includes 95% of termini of norm grads.

Fig. 6.—Illustrating the relationship with respect to the triaxial reference system of 100 points. Each point indicates the position of the terminus of G , as measured from a presumably normal electrocardiogram recorded from an adult subject with no clinical evidence of heart disease. (Bayley, R. H., Holoubek, J. E., and Holoubek, A. B., 1940.) See text.

Let us again consider Subject A. The vector \hat{H} lies in that half of the fifth sextant which is adjacent to the sixth. Let us now suppose that both \hat{A}_{QRS} and \hat{G} are found to lie along the positive axis of RL , and that the magnitude of \hat{G} is one-third greater than that of \hat{A}_{QRS} . Here, T_1 and T_2 are positive and T_3 is inverted. So far as the T waves are alone concerned, they appear to be normal. Actually, however, a decided abnormality is present. In the first place, \hat{A}_{QRS} shows the same abnormality (a rotation) as previously described, and the interpretation is the same. In the second place, the apparently normal T waves are actually abnormal because of the presence of secondary changes which have been annulled by primary changes. The latter are evidenced by a growth and positive rotation of \hat{G} with respect to \hat{H} . The interpretation of the gradient growth and rotation will not be considered at this point. However, had not the positions of \hat{A}_{QRS} and \hat{G} been considered with respect to \hat{H} , the anatomic axis of the ventricles, a diagnosis of a normal electrocardiogram might have been made, as in the case of Subject B.

When the area under a T deflection is small, the deflection is either low or diphasic. When the area under T is zero, the deflection may not exist, or it may be diphasic or even triphasic.

It may be noted that the term "axis deviation" has thus far been avoided. In my opinion, the current use of the term is more harmful than helpful. A so-called axis based upon the amplitudes of the QRS deflections and expressed as deviated with respect to the triaxial reference system can have little or no accurate interpretative value. The three manifest mean axes \hat{A}_{QRS} , \hat{A}_T , and \hat{G} are of equally great importance, and must be described in direction and magnitude, both with respect to the triaxial reference system and with respect to the base-apex axis \hat{H} . Moreover, "deviation" of a mean axis may be one of direction and magnitude, singly or in combination, away from or toward, an expected normal position. The terms adopted here are "diversion," indicating a change away from the normal in magnitude and direction, singly or in combination, and "reversion," indicating a change toward the normal in magnitude and direction, singly or in combination. In the event of diversion or reversion, it is necessary to state the specific axis with respect to which the diversion or reversion has taken place. Depending upon the circumstances, it may be found most convenient to change from one axis of reference to another. In the foregoing example of Subject A, the mean axis abnormality is most conveniently described (in the first instance) as a positive diversion of \hat{A}_{QRS} with respect to \hat{H} , and (in the second instance) as a positive diversion of \hat{A}_{QRS} and \hat{G} with respect to \hat{H} .

All of the polar angles which the various mean axes and reference axes make with respect to one another are subtended at the origin O of the triaxial reference system, and are described as positive or nega-

tive, depending upon whether the direction of measurement appears counterclockwise or clockwise, respectively. The term "rotation" of a mean axis implies a change of direction only, and the direction of rotation is positive or negative, depending on whether its motion appears counterclockwise or clockwise to an observer looking toward the frontal plane from a point anterior to the plane.

SECTION V

ON PRIMARY T-WAVE CHANGES

As described in the previous section, all primary T-wave changes are caused by a local alteration in the normal lack of uniformity of duration of the excited state in the subepicardial and subendocardial muscle layers of the ventricles. At the present time no understanding has been reached regarding the fundamental reason for the normal lack of uniformity of the effective duration of the excited state. It is clear, nevertheless, that the lack of uniformity in question is local, and exists at the epicardial and endocardial surfaces of the ventricular muscle. Moreover, the duration of the excited state in muscle units between the surface layers is immaterial. The normal ventricular gradient has a base-apex direction,¹⁷ and is said to point away from regions of the subepicardial and subendocardial muscle layers in which the average duration of the excited state is greatest, toward regions at these surfaces where the average duration is least. Consequently, the normal gradient may mean that the average duration of the excited state is greatest in the subepicardial, as compared with the subendocardial, muscle; it may mean a greater average duration of the excited state in the basal, as compared with the apical, muscle units subjacent to the ventricular surfaces; or, it may mean a combination of these possibilities. Certain phenomena concerned with the motions of the normal manifest mean axes have led some investigators¹⁸ to believe that the spatial gradient SG has a posterior as well as an apical direction. If this opinion is correct, the spatial gradient may mean that the average duration of the excited state is greater in the surface muscle units of the anterobasal regions, as compared with the posteroapical regions of the ventricular walls. It is likewise clear that, until more is known about the factor or factors which account for the normal ventricular gradient, little progress can be expected concerning the fundamentals of the abnormal gradient.

In view of the foregoing statements, it might be concluded that little of practical clinical value is to be found in the present discussion. Such is emphatically not the case. There are a number of varieties of factors which are known to operate clinically in such a manner as to alter the normal gradient and thus bring about primary T-wave changes. Often it is a difficult matter for the clinician to decide which factor or group of factors is operating to produce the particular primary T-wave changes under consideration. When more than one factor is known to be present,

attempts can be made to remove one factor at a time during a careful study of the concurrent serial electrocardiograms. In this rather tedious manner, reliable decisions can be reached regarding the interpretation to be placed upon many of the primary T-wave changes. Routine interpretations of primary T-wave changes are to be made, therefore, with great caution.

Among the factors which may alter the gradient singly or in combination are variations of the blood hydrogen ion concentration, various hormones, temperature, anemia, toxic agents, drugs of various kinds (digitalis, in particular), and local ventricular ischemia. Only the last of these factors is considered in the discussion which follows.

In general, there appear to be two important kinds of local ventricular ischemia, acute and chronic. Evidence of either kind may be present in the electrocardiograms from a subject who has no cardiac pain. On the other hand, a history of cardiac pain is characteristically present in subjects whose electrocardiograms display evidence of acute local ventricular ischemia. Subjects whose electrocardiograms display evidence of chronic local ventricular ischemia frequently give a history of recurrent attacks of paroxysmal dyspnea. The electrocardiographic changes ascribed to acute local ventricular ischemia do not differ materially in kind from those ascribed to the chronic form of local ventricular ischemia. In fact, the only significant differences are the rate of appearance, the duration, and the rate of disappearance of the T-wave changes. In the acute variety, the appearance is usually a matter of minutes, hours, or a few days; the duration is usually a matter of minutes, days, or a few weeks at the most; and the rate of disappearance is comparable to the rate of appearance. In the chronic variety, the appearance is a matter of a few or many months; the duration is a matter of many months or a number of years; and the disappearance is often interrupted by death. It is known that the acute variety may be evidenced electrocardiographically for as long as two weeks in man, without the involved muscle showing any gross or microscopic abnormalities.¹⁹ The chronic variety may indicate a concurrent development of myocardial fibrosis. In both varieties of local ventricular ischemia, the associated varieties of heart disease are hypertensive, syphilitic, and arteriosclerotic, singly or in combination. The acute variety is most commonly encountered in the arteriosclerotic type of heart disease. There can be little doubt that spasm of a subdivision of the coronary arterial tree is at least a precipitating factor in many of the instances of acute or transitory local ventricular ischemia. A somewhat subacute form frequently develops and disappears concurrently with the transitory hypertension of acute nephritis. Here, the electrocardiographic evidence is, strangely enough, of a kind strikingly similar to the chronic variety associated with chronic hypertension. Moreover, if the evidence in either instance may be interpreted as indicating local ischemia, it indicates, more strangely still, a local involvement of the

muscle ordinarily irrigated by the left coronary artery (see following analytical explanation).

The precise location and the intensity of the ischemia are the chief factors which determine the kind and magnitude of the associated T-wave changes. These primary T-wave changes are caused by a local prolongation of the average duration of the excited state in the neighboring surface muscle layers. Consequently, local ischemia which is confined to muscle between the surface layers is without associated electrocardiographic changes.

The muscle layer subjacent to the endocardial surface differs in two important respects from the layer subjacent to the epicardial surface. The former is nourished by a comparatively rich arterial plexus.²⁰ Moreover, when the local intravascular pressure falls because of impaired coronary flow, the subendocardial muscle layer is irrigated by blood from the ventricular cavity, i.e., blood which flows through the thebesian veins. It is conceivable that the innermost layer of muscle cells may obtain adequate nourishment by direct imbibition across the endocardium. It is clear, therefore, that, as a large zone of local ventricular ischemia develops and reaches transmural proportions, the intensity of the ischemia tends to be greater in the subjacent epicardial, than in the subjacent endocardial, muscle. Because of the lamellar character of the regression wave, the measured degree of the local ischemia is proportional to the difference between the degree of the local ischemia at the epicardial and that at the endocardial surface. With the development of local ischemia, the gradient undergoes a diversion which tends to bring the direction of the vector \vec{SG} into that of a line drawn from the center of the local ischemia toward the center of the involved ventricle. Generally, then, if local ischemia involves that portion of the ventricular muscle which is ordinarily irrigated by the right coronary artery, the manifest gradient \vec{G} sweeps through a positive rotation¹⁹ into the first, or the neighboring half of the second, sextant. Let us assume that \hat{A}_{QRS} retains its normal position in the sixth sextant (Fig. 7, *a*). The vector \hat{A}_T , when altered by the described diversion of \vec{G} , is now such as to measure a small positive or zero area under T_1 , and equally large negative areas under T_2 and T_3 . If the local ischemia involves that portion of the ventricular muscle which is ordinarily irrigated by the left coronary artery, the manifest gradient \vec{G} sweeps through a negative rotation into the fifth or the adjacent half of the fourth, sextant.¹⁹ Let us again assume that \hat{A}_{QRS} retains its normal position in the sixth sextant (Fig. 7, *b*). The vector \hat{A}_T , as altered by the described diversion of \vec{G} , is now in a position which measures a large negative area under T_1 , an equally large positive area under T_3 , and a zero or nearly zero area under T_2 . When the areas under the T waves are large (positive or negative), the effective events of regression may begin before those of accession are complete, and the RS-T junction is

displaced from the base line of the curve in the direction of the regression effect. RS-T junction displacements of this kind are not to be confused with those ascribed to injury (see next section).

In so far as the general form of the T wave is concerned, there are no important differences between those changes ascribed to uncomplicated local ischemia and those ascribed to the perifocal ischemia of infarct. As a matter of fact, the acute variety of the former changes occasionally heralds ventricular infarction, and the primary T-wave changes disappear temporarily as a result of the development of injury effects. Subsequently, the same T-wave changes reappear subtotally as evidence of the perifocal ischemia of infarct. The injury effects (RS-T junction displacements) concurrently vanish with the reappearance of local ischemia effects. An example of the final appearance and disappearance of the changes ascribed to the perifocal ischemia of infarct is shown in Fig. 7, *c*. The associated path traced out by the terminus of the manifest gradient \bar{G} is shown in Fig. 7, *d*.

In the semiunipolar and unipolar leads, the relative delay of regression at the epicardial surface subjacent to the exploring electrode is evidenced by a sharp inversion of the T deflection. With anterolateral ischemia, this effect may be shown in curves recorded at the fourth, fifth, and sixth precordial positions.

Strictly apical ischemia at first shortens the gradient, and, if sufficiently intense, may reverse it into the third sextant. The former gradient change tends to reduce the positive areas under the normally upright T deflections, whereas the latter change may account for sharp inversion of T_1 , T_2 , and T_3 , together with inversion of T at the fourth precordial position. During the development of a gradient reversal of this kind, T_1 , T_2 , and T_3 become inverted before the actual gradient reversal occurs. If \hat{A}_{QRS} and \bar{G} are collinear in the sixth sextant, \hat{A}_T appears in the third sextant as the magnitude of \bar{G} becomes less than that of \hat{A}_{QRS} .

Finally, it is conceivable that a diffuse ischemia, localized to the basal regions of the ventricular walls, might produce an excessive increase in the magnitude of the normal gradient without altering its normal direction. The normally positive areas under T_1 and T_2 would be increased accordingly. In one instance of this kind the magnitude of the gradient measured 160 m.v.s. The curve appeared essentially normal in all other respects. The patient had had typical attacks of cardiac angina throughout the month which preceded the recording. For an example of electrocardiographic changes ascribed to local ischemia, see Fig. 8, *a* and *b*.

The problem of local ventricular ischemia, as depicted in this section, is incomplete to the extent that injury and blocking effects, which are ascribed to a second and more severe grade of impaired blood supply, have not been dealt with (see next section).

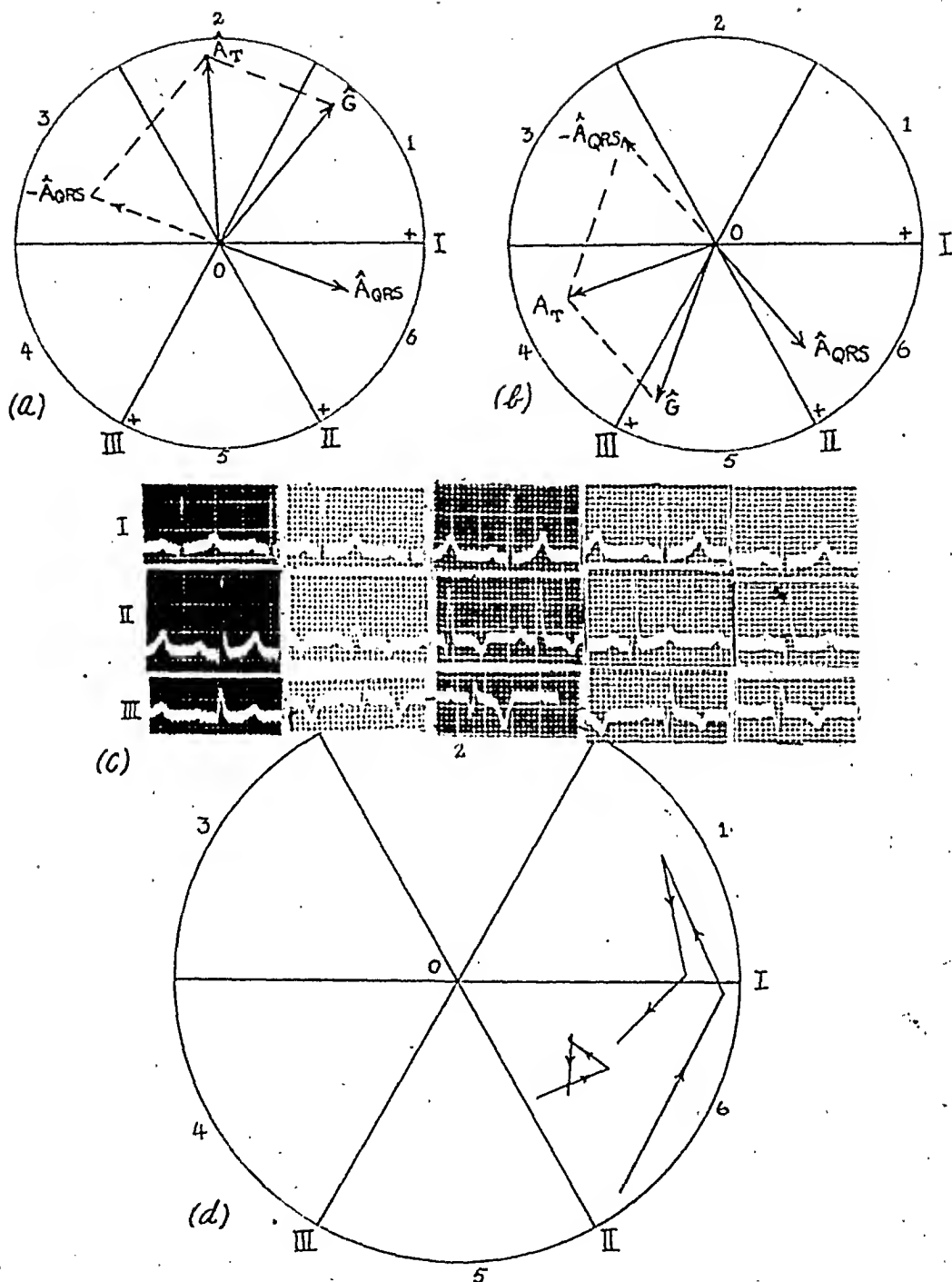


Fig. 7.—(a) Showing the manifest mean axes in the positions considered characteristic of local ventricular ischemia of the muscle that is ordinarily irrigated by the right coronary artery. (b) Showing the manifest mean axes in the positions considered characteristic of local ventricular ischemia of the muscle which is ordinarily irrigated by the left coronary artery. (c) Five serial electrocardiograms recorded over a forty-day period from a subject who had had recent posterior infarction. The left-hand curve was recorded before, and the remaining curves after, infarction. QRS is of the $R_1Q_2Q_3$ variety. Note the appearance and disappearance of primary T-wave changes ascribed to the zone of perifocal ischemia. (d) The path restricted to the sixth sextant is that described by the terminus of \hat{A}_{QRS} throughout the forty-day period over which the serial curves in (c) were recorded. The path restricted to the sixth and first sextants is that traced out by the terminus of \hat{G} as the gradient undergoes the final diversion and subsequent reversion during the same forty-day period. See text.

SECTION VI

ON THE INJURY EFFECT AND ITS RELATIONSHIP TO
MYOCARDIAL INFARCTION

According to the notation hereinbefore adopted, the ventricular regression effect "writes" the T $s\hat{E}$ -loop of the three-dimensional vectorcardiogram, and the T \hat{E} -loop of the two-dimensional vectorecardiogram. The latter is the projection of the former upon the plane of the triaxial reference system. Moreover, the T $s\hat{E}$ -loop is the path described in space by the terminus of $s\hat{E}$, the instantaneous axis of regression. The relationship between these loops and the T deflections of the extremity leads is the same as that previously described as connecting the QRS loops with the initial ventricular deflections of the extremity leads. Regression of the auricles also produces a measurable effect in the vectorcardiogram and in the extremity leads, but the effect is ordinarily obscured by the deflections of ventricular accession.

In man, the RS-T junction, as seen in the precordial leads, is often displaced upward normally from the base line for a distance of one or two millimeters, indicating that a regression effect has already commenced at the time at which accession terminates. For the most part, however, the regression effect does not manifest itself in the extremity leads until the lapse of a variable short interval of time after accession terminates. This interval constitutes the so-called RS-T segment, which is written on or nearly on the base line of the curve.

It is clear that the onset of T in the extremity leads does not represent the onset of ventricular regression, but merely the time at which the magnitude of the regression effect is sufficiently great to affect the completed record. Under certain circumstances the magnitude of early regression is sufficiently great to affect the completed record at the time at which ventricular accession ends. Whenever this is the case, the RS-T segment is absent, and the onset of T appears to take off from the final ascending or descending limb of QRS. In reference to this event, the RS-T junction is said to be displaced above or below the base line. If the duration of QRS is prolonged (as in bundle branch block), the RS-T segment is characteristically absent and the junction is often displaced. Early regression and prolonged accession are likely to occur together in effecting an RS-T junction displacement. Junction displacements caused by these factors operating singly or in combination are referred to as displacements of the permanent type, in contrast to a temporary variety which is associated with the injury phenomenon of ventricular muscle. The permanent variety may ordinarily be recognized by its association with QRS complexes which have large areas under the curve, and by the fact that the direction of the displacement is like in sign to that of the area under T, the adjacent deflection.

It is the purpose of the present discussion to deal with the temporary variety of RS-T junction displacement which is associated with injury

of ventricular muscle. The term injured muscle, as used throughout the discussion, implies an altered physiologic, rather than an altered structural, change. The alteration is recognized by the associated electrocardiographic changes, which, in a given case, may or may not prognosticate detectable structural change. As ordinarily observed in connection with disease of the coronary arteries, the zone of injured muscle is ischemic in the sense that its blood supply is insufficient, and, except for the degree of this insufficiency and the electrical effects produced, it resembles a zone of local ischemia, as described in Section V. The injured zone is regarded as a second and more severe grade of local ischemia. Obviously, the two grades are closely related, and, depending upon the circumstances, one grade may pass into the other. In a given curve, almost any combination of the associated effects may be encountered.

In Section V, a zone of local ischemia was described as characterized by a local prolongation in the effective duration of the excited state, or by a local, tardy onset of regression. The next grade of impaired function quite naturally appears to be an inability to complete locally the delayed regression process. In terms of the membrane theory, a subnormal regression process of this kind constitutes a tardy subnormal change of polarization on regression throughout the injured zone. In general, the electrical effects which are produced depend upon the location of the injured zone with respect to the ventricles as a whole, upon the distribution of the injured zone with respect to the epicardial and the endocardial surfaces, and upon the degree of subnormality of the change of polarization throughout the injured zone.

ON THE EFFECTS OF AN INJURED LAMINA

The experimentally injured region of the epicardial surface of the ventricles, or the region of local or diffuse pericarditis takes the form of a thin, shell-like lamina of injured cells at the periphery of the damaged area. The lamina separates the damaged region from the surrounding normal muscle. Because of the subnormal change of polarization which occurs on regression of the injured lamina, there exists, during diastole, a gradient in the intensity of polarization throughout the injured lamina. In any element of the lamina, the direction of gradient increase is perpendicular to the surfaces of the injured element in a direction away from the damaged toward the normal muscle. Consequently the injured lamina acts electrically, during diastole, like a steady double-layer, with its source surface adjacent to normal, and its sink surface adjacent to damaged, muscle.¹⁵ Familiarity with the considerations advanced in Sections I and II concerning the character of the field produced by an electrical double-layer enables the immediate formation of an expression which describes the potential V'_1 at any point p in the conductor near the injured region. We have

$$(6-1) \dots V'_1 = \phi'_1 \Omega_1$$

where ϕ'_1 is the electrical moment during diastole of the injured lamina, and depends upon the difference of the intensity of polarization at the two lamellar surfaces, one adjacent to the damaged, and the other adjacent to the normal, muscle; and where Ω_1 is the solid angle subtended at p by the boundary of the injured lamina. Unless the damaged region extends entirely through the ventricular wall, as might be the case for a stab wound, the boundary of the injured lamina resides at the epicardial surface. Moreover, Ω_1 is positive or negative (during diastole), depending on whether an observer stationed at p , and looking through the cone, views the injured lamina through *normal* or through *damaged* muscle.

Let us now examine the potential at p during systole or during the excited ventricular state. Accession constitutes the initial reversal of polarization; consequently, except for a new intensity of polarization at the surfaces of the injured lamina and the reversed polarity of the injured lamina, the source-sink distribution of the field of injury is unchanged during systole. Thus, if V''_1 denotes the injury potential at p during systole, and if ϕ''_1 denotes the electrical moment of the injured lamina during systole, we have

$$(6-2) \dots \quad V''_1 = \phi''_1 \Omega_1$$

where Ω_1 is now positive or negative, depending on whether an observer stationed at p , and looking through the cone, views the injured lamina through *damaged* or through *normal* muscle. When the galvanometer is standardized during diastole a compensating current is introduced into the body-galvanometer circuit which neutralizes the effect during diastole of an injury current. Consequently, during systole, when the flow of injury current reverses, the compensating current is left free to flow around the circuit with the systolic injury current. The total effect on the completed record occurs, therefore, only during systole, and consists of the sum of two currents, one described by the right-hand side of eqn(6-1), with the sign changed, and the other described by the right-hand side of eqn(6-2). Consequently, the injury potential V_1 at p , as depicted by the completed record, is given by

$$(6-3) \dots \quad V_1 = (\phi'_1 + \phi''_1) \Omega_1,$$

and if in this expression we define the content of the parentheses by ϕ_1 , we have

$$(6-3) \dots \quad V_1 = \phi_1 \Omega_1$$

for use in the description of the injury potential produced at the tip of the exploring electrode by the presence of an injured lamina.

Relation (6-3) has a number of important and simple applications. In acute diffuse pericarditis, which damages the subepicardial muscle layer, the injured lamina has a free edge, or boundary, encircling the base of the ventricles, whereas the configuration of the outer surface

of the injured lamina is very nearly that of the ventricular epicardium itself. At all points within, or at, the surface of the conductor outside the heart, and on the inferior side of a plane passed through the boundary of the injured lamina, the injury potential is positive; at all points within, or at, the surface of the conductor on the other side of the plane, the injury potential is negative; at points within, or at, the surface of the conductor and within the specified plane outside the boundary of the injured lamina, the injury potential is zero; and, finally, at all points within the plane inside the boundary of the injured lamina, the injury potential is $-2\pi\phi_i$. Within the heart the injury potential is negative.

In dealing with the injured lamina in regard to its effect on the RS-T junctions of the extremity leads, we are at liberty to construct during systole the spatial axis of injury $s\hat{E}_i$, and its projection \hat{E}_i , upon the plane of the triaxial reference system in a manner similar to that used in dealing with the spatial and manifest axes of accession. Thus $s\hat{E}_i$ is given by the relation

$$(6.4) \dots \quad s\hat{E}_i = S_i\hat{e}_i$$

where S_i is the plane area circumscribed by the boundary of the injured lamina, and polarized in the same sense as the injured lamina is polarized during systole, and where \hat{e}_i is a unit vector in the direction of the outward-drawn normal to the positive surface of S_i . Relation (6.4) shows that the magnitude of the vector $s\hat{E}_i$ is equal in units of length to the area of S_i in units of area, and is, moreover, independent of the configuration of the surfaces of the injured lamina. In the case of acute diffuse pericarditis, S_i lies at the ventricular base, with its positive surface directed toward the ventricular apex. Consequently, $s\hat{E}_i$ is collinear with the anatomic axis \hat{H} , and the vector \hat{E}_i splits the sixth sextant. Clearly, the measured injury potential is a concordant positive displacement of the RS-T junctions of all extremity leads, large in Lead II, intermediate in Lead I, and small or zero in Lead III. It may be observed further that a local pericarditis which caps the ventricular apex produces the same, or nearly the same, effects as described for diffuse pericarditis. A localized pericarditis on the anterolateral aspect of the ventricles produces positive RS-T junction displacements in precordial leads at positions 4, 5, and 6, and discordant displacements in the extremity leads, upward in Lead I and downward in Leads II and III. As will be shown presently, these are precisely the kind of injury effects observed in recent anterolateral infarction.

The dictates of eqn(6.4) may be used to formulate a rule which is useful in anticipating the injury effects of the extremity leads. i.e., the spatial axis of injury $s\hat{E}_i$ points during systole in the direction of a line drawn from the center of the involved ventricle toward the center or centroid of the injured region, whereas the magnitude of $s\hat{E}_i$ is pro-

portional in length to the area circumscribed by the boundary of the injured lamina.²¹ Moreover, the projection of $s\hat{E}_i$ upon the triaxial reference plane gives the manifest axis of injury \hat{E}_i , which defines by its projections upon the reference axes the direction and proportional magnitude of the RS-T junction displacements of the extremity leads. Thus, in the case of acute diffuse pericarditis, the configuration of the injured lamina is such that the centroid lies between the center of the ventricles and the cardiac apex. In connection with further use of the rule, it is important to note that a localized pericarditis, confined to the strictly anterior aspect of the ventricles or to the strictly posterior aspect of the ventricles, produces an axis of injury $s\hat{E}_i$ which is directed normal to the plane of the triaxial reference system. Consequently, \hat{E}_i is zero and no RS-T junction displacements appear in the extremity leads. It also follows that two areas of acute local pericarditis, confined to diametrically opposite aspects of the ventricular walls, are associated with two axes of injury, like in magnitude and unlike in sign (or of inverse direction). Their resultant is zero, and no associated RS-T junction displacements appear in the extremity leads.

Let us conclude the present argument with the example of stab wound of the ventricles. The injured lamina conforms in its configuration to that of the surface of the penetrating instrument (provided no important subdivision of the coronary arteries is severed). If penetration of the wall is subtotal, the boundary of the injured lamina conforms to the hole in the epicardial surface. Obviously, because of the size of the instruments ordinarily used, S_i is small, and, consequently, $s\hat{E}_i$ is small, so that the anticipated RS-T junction displacements of the extremity leads are likely to be negligible. If penetration of the wall is total, the injured lamina has a tubular configuration, with a boundary at the epicardial, and a boundary at the endocardial, surface. Moreover, the boundaries are approximately similar geometrically. When each boundary is treated separately, as if the other opening of the injured lamina were closed, two forces are derivable which are like in magnitude and unlike in sign (of inverse directions). Their resultant is zero, and, consequently, total, as compared with subtotal, penetration is less likely to produce RS-T junction displacements in the extremity leads. When striking displacements are found before operation, it is best assumed that an important subdivision of the coronary arteries is severed. The subepicardial muscle is very susceptible to trauma, and may act as if it were injured when the epicardial surface is handled gently or even wiped with moist gauze. Under the circumstances, the circumferences of the injured laminae are large, and the electrical effects that are produced may be striking. However, the trivial nature of such injuries results in effects of brief duration, and striking RS-T junction displacements may vanish in a few hours or even in a few minutes. These factors are considered essential for proper interpretation of electrocardiograms from subjects with stab wound of the heart.

ON THE ELECTROCARDIOGRAPHIC EVOLUTION OF
MYOCARDIAL INFARCTION

The QRS changes associated with myocardial infarction have been ascribed to the absence during systole of the electrical forces which were previously present in the dead zone. It is necessary to modify this statement at the present time. Fundamentally, two kinds of QRS changes are ordinarily associated with myocardial infarction, i.e., transient and permanent. The latter are ascribed to the absence of forces that were previously present in the dead zone. Throughout the injured zone, regression consists of a subnormal change of polarization.²¹ Consequently, the electrical moments of that subdivision of the accession wave which passes through the injured zone are of reduced magnitude as long as the injured zone persists. Ultimately, part of the injured zone may die and thus increase the dimensions of the dead zone and the magnitude of the permanent QRS changes. In many instances it is highly probable that most of the injured zone vanishes by passing into the ischemic state. Transient QRS changes associated with infarction are ascribed to the diminished magnitude of forces which had been previously great during accession of the injured zone. The subsequent disappearance of the injured zone is attended by the return to normal magnitude of accession forces that were previously small throughout the injured zone. Concurrently, there occurs a subtotal return of QRS changes toward a more normal form.

In the initial stages of impaired coronary flow, the region of diminished irrigation may pass at once into first grade ischemia. The electrocardiogram at this time reveals only striking primary T-wave changes (Fig. 8, *a*). At a variable period of time thereafter, the more central regions of the zone of first grade ischemia pass into second grade ischemia or into the injured state. Provided the injured zone extends to the epicardial surface, RS-T junction displacements of injury appear in the completed record. Potentially transient QRS changes concurrently develop. Inasmuch as the development of the injured zone is dependent upon subtotal conversion of the ischemic zone, the early primary T-wave changes subtotally disappear (Fig. 8, *b*). If the patient is fortunate, normal coronary flow may be re-established, whereupon the injured zone returns to the ischemic state and the latter subsequently vanishes (Fig. 8, *a*). Throughout such a period, the clinical phenomena which are associated with death of heart muscle (fever, leucocytosis, increased sedimentation rate, and fall of blood pressure) are absent. In more unfortunate subjects infarction develops, whereupon extension of the injured zone continues until only a small semiperifocal zone of ischemia remains. Thus, striking RS-T junction displacements appear, together with more definite QRS changes, and the initial primary T-wave changes may now be absent except in unipolar or semipolar leads recorded with the exploring electrode super-

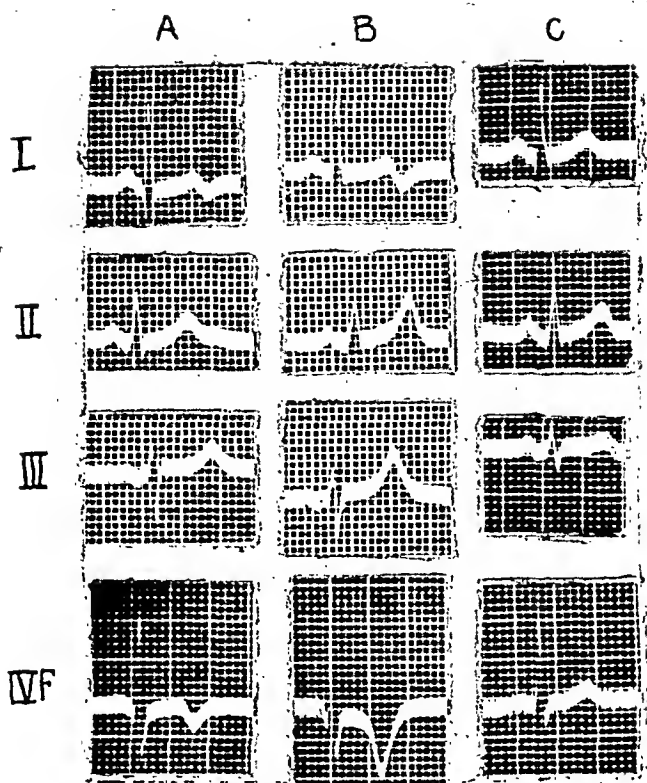
jacent to the zone of local ischemia. In similar leads recorded with the exploring electrode superjacent to the injured zone, the RS-T junction displacements are maximal and positive.

The reasons for a relatively limited extension of the injured zone in the direction of the neighboring endocardial surface are the same as those which determine a like distribution of local ischemia, and are set forth in Section V. At such a time, when the injured state involves a maximal area of subepicardial muscle and the neighboring subendocardial muscle is as yet uninvolved, the magnitude of the RS-T junction displacements is maximal. At some critical stage of extension of the injured zone, death of its more central regions occurs. At this time the clinical picture of acute infarction is complete. The severity of the clinical manifestations depends upon the rate of development of the various stages and to a less extent upon the volume of muscle involved. The dead zone may remain stationary or extend beyond its initial size. In event of the latter, the associated QRS changes progress.

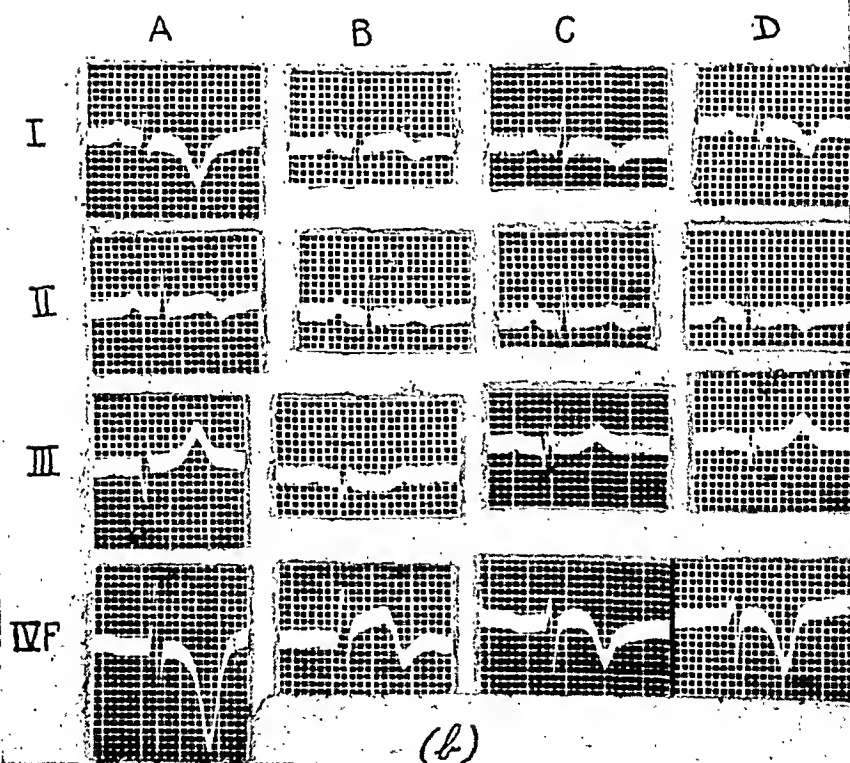
During the early stages of healing (ordinarily two to four weeks after infarction in man), the injured zone diminishes in the direction of the dead zone because of the passage of its peripheral units from the injured, back into the ischemic, state. Consequently, when the injured zone is no longer in contact with the epicardial surface, the RS-T junction displacements will have vanished, together with most of the temporary QRS changes. Inasmuch as the subepicardial units of the ischemic zone have been increased by conversion of injured units into the ischemic state, the associated primary T-wave changes subtotally reappear. Finally, during the months which follow, the ischemic zone diminishes in the direction of the dead zone because of the gradual return of its units to the normal state. Concurrently, the final primary T-wave changes vanish, and only the permanent QRS changes, associated with the dead region, remain. Certain of the foregoing statements need clarification, but before entering the more profound aspects of the problem it is suggested that the reader refer to Fig. 9 for a diagrammatic summary of the critical stages of infarction.

At the present time it is not generally recognized that, from a fundamental standpoint, stages *A* through *B* of Fig. 9, *a* constitute the

Fig. 8.—(a) Primary T-wave changes of local ventricular ischemia: Curves A and B were recorded, ten days apart, from a 40-year-old subject who was hospitalized at the time because of severe heart pain. There are no definite changes which can be ascribed to muscle in the injured or in the infarcted state. The local ischemia is more intense at the time of the B recording, where the manifest gradient has undergone a striking negative rotation. The ischemia is anterolateral or in the muscle ordinarily irrigated by the left coronary artery. The subject had no fever, leucocytosis, fall of blood pressure, or increased sedimentation rate. Curve C was recorded after an asymptomatic interval of two months, and is regarded as normal. (b) Primary T-wave changes and RS-T junction displacements, with minor QRS changes, in a subject who had no clinical evidence of myocardial infarction: The subject, 42 years of age, had suffered severe heart pain throughout the twelve-day period over which curves A, B, and C extend. Curve D was taken one week after C, at a time when pain was absent. Curve A is typical of anterolateral ischemia. In curve B, at the time of maximal pain, a definite injury effect is present in Lead IVF. Here the primary T-wave changes have subtotally disappeared. Throughout curves C and D the injury effects vanish, and the T-wave changes again become pronounced. It is held that the subject narrowly missed having myocardial infarction at the time of the B recording.



(a)



(b)

Fig. 8.—(For legend see opposite page.)

physiologic basis of the early myocardial changes associated with infarction. The electrocardiographic changes which accompany stages *A* and *B* consist of primary T-wave changes caused by acute local ventricular ischemia, and, as previously pointed out (Section V), are the result of a diversion of the gradient. In stage *B*, a zone of injury has appeared without affecting the completed record. Fig. 9, *c* illustrates the manner in which the zone of acute (or chronic) local ventricular ischemia may be treated for purposes of analysis. The zone of local ischemia is limited at first by the interface which separates it from normal muscle. After further expansion it becomes limited, in addition, by the epicardial surface. If and when the ischemic zone extends to the endocardial surface, it is necessary that the circumference of its epicardial surface boundary exceed the circumference of its endocardial surface boundary in order that the average duration of the excited state within the former boundary shall exceed that within the latter boundary. The zone of ischemia is divided into lamellae of elementary thickness. Throughout any single lamina the duration of the excited state is uniform. If lines are drawn, commencing upon the periphery of the ischemic zone, inward toward the point or points of maximal ischemia, and are made to cut all encountered lamellar surfaces at right angles, the direction of the lines describes the direction of the most rapid space rate of increase of effective duration of the excited state. Neglecting the influence on regression produced by the local order of accession, the direction of the lines determines the direction of local regression. The negative regression potential at a point *p*, nearby, and outside the heart, may be regarded as proportional to the sum of the negative solid angles subtended at *p* by the epicardial surface boundaries of the open ischemic lamellae. If some of the lamellae are likewise open at the endocardial surface, the potential at *p* will be less negative by a value proportional to the sum of the positive solid angles subtended at *p* by the specified endocardial surface boundaries. Inasmuch as the solid angles which measure the regression potential are independent of the configuration of the surfaces of the lamellae whose boundaries subtend them, the regression potential at *p* depends only upon the second reversal of polarization of the surface muscle units. Regression of the lamellae which are closed or which lie between the surfaces makes no contribution to the regression potential outside the ventricular wall. In short, the regression potential at an instant is proportional to the difference of potential due to the change of polarization at the epicardial surface as compared with that at the endocardial surface. That a change of polarization is likewise present between these surfaces is immaterial.

In stage *A* (Fig. 9, *a*), when the zone of ischemia does not touch the epicardial or endocardial surface, all of the lamellae are closed. A zone of ischemia of this kind cannot alter the order of regression of the muscle units at the ventricular surfaces, an order which alone determines the form of T.²²

In Fig. 9, *d* the injured zone is treated in a fashion similar to that described for the ischemic zone. The lamellae into which the injured zone is subdivided represent regions throughout any one of which the subnormal change of polarization during regression is everywhere the same. If the subnormal change of polarization is regarded as having occurred initially during accession, rather than regression, the effect on the completed record is essentially the same, although the process is one of gradual blocking, and although no injury current flows. As pointed out elsewhere,²¹ it appears unlikely that a blocking process is the rule. The lines (Fig. 9, *d*) which commence upon the dead zone and radiate toward the periphery of the injured zone, and which cut all encountered lamellar surfaces at right angles are the paths along which there

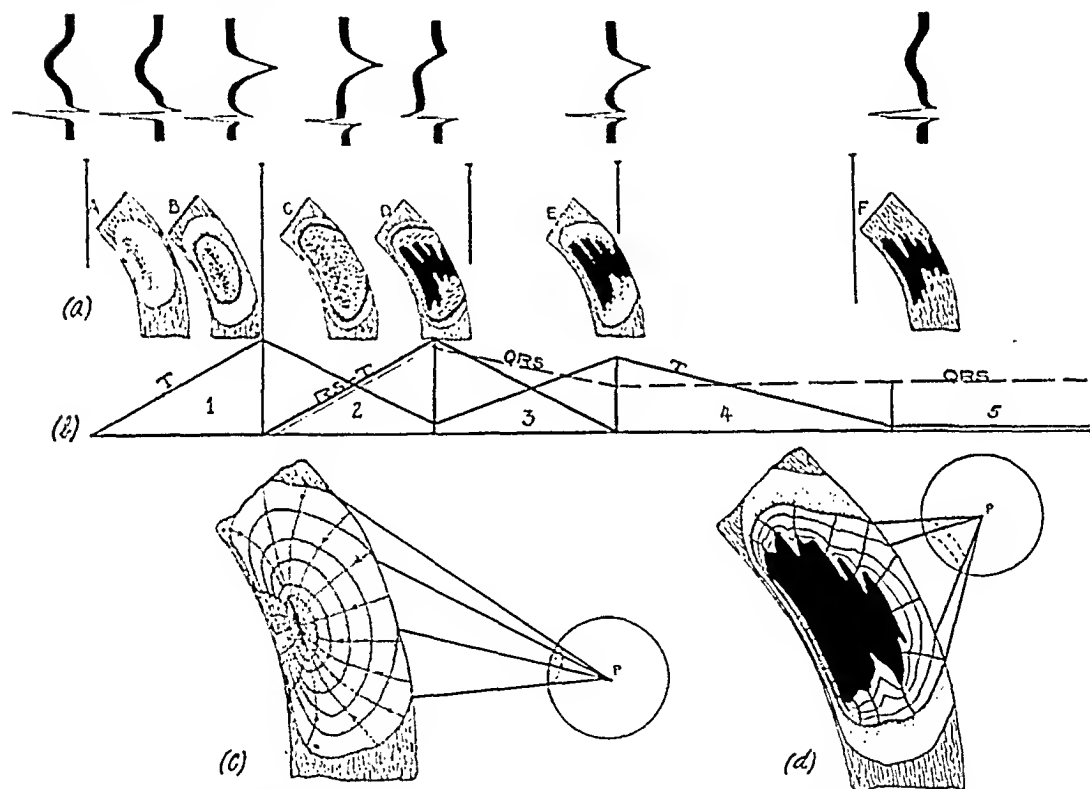


Fig. 9.—(a) Blocks of muscle A, B, C, D, E, and F depict the evolution ascribed to myocardial infarction. Superimposed are curves which display the associated electrocardiographic changes as produced in a unipolar lead from a superjacent point. In block A, local ischemia has developed without producing detectable electrical effects. In block B, ischemia has reached the epicardial surface and has accounted for a primary T-wave change. An injured zone has also appeared within the ischemic zone, and theoretically minor QRS changes may be present. In block C, the injured zone has reached the epicardial surface, so that RS-T junction displacements, further QRS changes, and reduced T-wave changes are present. In block D, infarction has occurred, and RS-T junction displacements are maximum. Concurrently, the primary T-wave changes are reduced to a minimum. In block E, healing has commenced. The injury zone has vanished and the effects of local ischemia are again pronounced (compare curves three and six from the left). In block F, the infarct is depicted as healed. No perifoetal ischemia is present. (b) Diagram showing the time relationship of the appearance and (or) disappearance of the various kinds of electrocardiographic changes, QRS, T, and RS-T junction, which characterize the electrocardiographic evolution of myocardial infarction. Note the reciprocal relationship between primary T-wave changes and RS-T junction displacements, which is likewise shown by the development, at the epicardial surface, of the two zones, ischemic and injured. See text. (c) Showing the lamellar character of the ischemic zone and its relationship to the regression potential produced at a superjacent point p. (d) Showing the lamellar character of the injured zone and its relationship to the injury potential produced at a superjacent point p. See text.